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# Malaysian Journal of Ophthalmology

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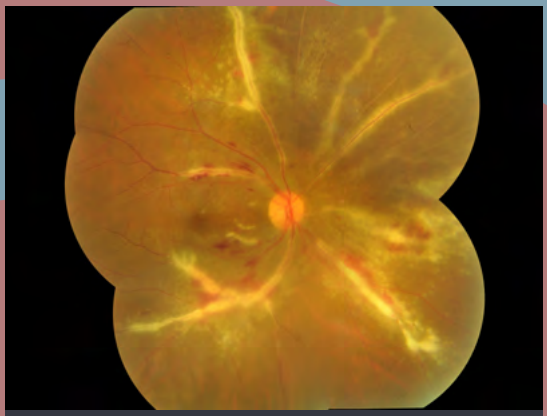

ABOUT THE COVER IMAGE

*Spiral firework* features a case of cytomegalovirus retinitis. The image is courtesy of Safinaz Mohd Khialdin, lecturer and ophthalmologist at the Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia.

# Malaysian Journal of Ophthalmology

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## Original articles

Malaysian Journal of Ophthalmology


*Editorial*
*https://doi.org/10.35119/myjo.v3i3.247*

# Meeting polypoidal choroidal vasculopathy treatment needs halfway

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Polypoidal choroidal vasculopathy (PCV) is a subtype of neovascular age-related macular degeneration (nAMD) that accounts for up to 50% of nAMD cases in Asia.[1] The PCV complex comprises polypoidal lesions (PL) and branching neovascular network (BNN), both of which are found between the retinal pigment epithelium (RPE) and the outer portion of Bruch's membrane.[2] Hence, PCV should be considered a variant of type 1 neovascularization.[3] In addition, studies of the choroidal background suggest PCV resides within the pachychoroid spectrum of diseases, characterized by choroidal thickening, dilated Haller's layer vessels, and attenuation of the overlying choriocapillaris.[4]

Vision loss in PCV may occur via several mechanisms, including exudation and haemorrhage.[2,3] While anti-VEGF monotherapy has been demonstrated to reduce retinal thickness, closure of PLs is often desired as unclosed PLs are often the source of hemorrhage.[2,5,6] Photodynamic therapy (PDT) has been shown to be superior to ranibizumab monotherapy in resulting in closure of PLs in the EVEREST and EVEREST II studies.[5] On the other hand, anti-VEGF monotherapy has been shown to be effective in preserving vision in PCV patients, but its ability to close PLs appears variable.[7]

In the EVEREST II study, combination therapy with PDT was superior to ranibizumab monotherapy in achieving closure of PLs.[55] The combination arm also required less retreatment. However, in clinical practice, some concerns remain regarding the potential adverse effects of full-fluence PDT, which may include choroidal ischemia and RPE disruption. Severe vision loss following full-fluence PDT has been reported in approximately 1% of cases.[8] In light of this risk, modified PDT, either as half-fluence PDT (hfPDT; light dose of 25 J/cm$^2$) or half-dose PDT

(hdPDT; 3 mg/m$^2$ verteporfin) have been attempted in the management of PCV.[6] In this issue, Chow and coworkers reported outcomes for hdPDT combination therapy and anti-VEGF monotherapy for PCV. In their retrospective case series, 6-month functional and structural outcomes were reported for eight eyes treated with hdPDT combined with ranibizumab or aflibercept, and for 10 eyes treated with ranibizumab or aflibercept monotherapy. The authors reported a trend towards better letter gains in the combination therapy arm, with similar anti-VEGF treatment burden in both groups. PL closure rate and choroidal thickness changes post-treatment were not reported. Perhaps counterintuitively, reduction in central subfield thickness was more marked in the monotherapy group, although not statistically significant. These somewhat conflicting findings may reflect the heterogeneity in lesion characteristics. As the authors have rightly pointed out, the combination group may have preselected patients with more aggressive PCV, or cases with more extensive disease or aggressive morphology. In the hdPDT group, there was also a mixture of deferred or prompt combination. This variation in timing of hdPDT may also affect the findings.

In addition to reporting vision outcome and treatment number, an additional endpoint which would be important to note in this study is the polyps' status. The speed of complete PLs closure rate can be evaluated as one of the biomarkers of treatment outcome. Patients with complete PL closure might require less anti-VEGF and thus reduce the treatment burden. Choroidal anatomy plays an important role in PCV pathophysiology, changes in choroidal thickness following hdPDT. Poorer anatomical response to loading dose in anti-VEGF in a thicker choroid have been reported.[9]

The current work by Chow and colleagues suggests the efficacy of hdPDT in PCV remains unclear, although a favourable safety profile was seen in their series. These results highlight the difficulty in generalizing treatment recommendations as PCV lesions are highly heterogenous. hdPDT combined with ranibizumab was previously reported to be effective for smaller PCV lesions but less effective in cases with BNN and multiple PLs.[10]

In real-world settings, complete regression of PLs is a desirable endpoint for patients with PCV as it decreases the frequency of retreatment and reduces the risk of devastating haemorrhage and chronic exudation. Several methods have been shown to decrease the rate of PLs, including prompt combination at baseline with either full-fluence or hfPDT, prolonged monthly loading with anti-VEGF for up to 6 months, or deferred combination with PDT. Future studies evaluating the efficacy and safety of these treatment modalities will need to carefully balance the baseline characteristics of PCV lesions and choroidal background. Longer follow-up design will also be necessary to evaluate any differential effect on recurrence rate. Until then, for clinical purposes, reviewing the indocyanine green angiography features at month 3 remains an important assessment, especially in persistent, recalcitrant, aggressive disease that progress despite initial monthly anti-VEGF therapy.

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Malaysian Journal of Ophthalmology


*Editorial*

# Best Original Articles and Best Case Reports 2019–2020

Dear readers,

We have selected the best original articles and case reports published in Malaysian Journal of Ophthalmology (MyJO) in 2019–2020. Our selection was based on scientific merit (40%), number of citations (40%), and number of downloads from the MyJO journal website (20%). The scientific merit score was conducted by a special panel elected by MyJO's Editorial Board.

We wish to thank all authors who have submitted to MyJO over the years for considering the journal a venue for their research. We look forward to your future submissions. Congratulations to all the winners!

**Malaysian Journal of Ophthalmology Editorial Board**

Malaysian Journal of Ophthalmology

# BEST ORIGINAL ARTICLE (2019-2020)

**1. Comparison of contrast sensitivity between three aspheric acrylic monofocal intraocular lenses: a prospective randomised trial**
*Chin Chiet Ying Alice, Banumathi Gurusamy, Lim Keat Andrew, Mae-Lynn Catherine Bastion*
Issue 1-4, 2019

**2. Infectious keratitis: findings from a retrospective review in the central zone of Sarawak**
*Koay Jiah Bou, Tan Teng Siew, Chua Ter Wei, Tan Li Mun*
Issue 1-3, 2019

**3. Low density lipoprotein receptor (LDLR) gene and ocular manifestation in Malay patients with familial hypercholesterolaemia**
*Ahmad Tajudin Liza-Sharmini, Nor Idahriani Muhammad Nur, Alyaa R Al-Khateeb, Wan Hazabbah Wan Hitam, Zilfalil Bin Alwi*
Issue 1-2, 2019

**4. A five-year retrospective hospital-based study of endogenous endophthalmitis in south Malaysia**
*Hayatulrizal Muhd, Ling Kiet Phang, Francesca Martina Vendargon*
Issue 2-1, 2020

**5. Ocular biometry and refractive changes post sutureless vitrectomy surgery**
*Raja Nor Farahiyah Raja Othman, Zabri Kamaruddin, Selva Raja Vengadasalam, Mushawiahti Mustapha*
Issue 1-2, 2019

Malaysian Journal of Ophthalmology

# BEST CASE REPORT (2019-2020)

**1. Bilateral optic perineuritis associated with p-ANCA vasculitis**

*Ivan Cheng En Yoo, Yong Meng Hsien, Mushawiahti Binti Mustapha, Jemaima Che Hamzah*

Issue 1-2, 2019

**2. Charlie ant insect bite-associated preseptal cellulitis**

*Patricia Ann John, Sylves Patrick, Qi Zhe Ngoo, Wan Hazabbah Wan Hitam, Adil Hussein*

Issue 2-2, 2020

**3. Sweet disaster: use of honey-based eye drops as an alternative treatment for vernal keratoconjunctivitis**

*Kenneth Teow Kheng Leong, Rebecca Jennifer Mary Louis, Lai Yin Peng, Rohanah Alias, Safinaz Mohd Khialdin*

Issue 1-2, 2019

**4. Reversal of impending central retinal vein occlusion secondary to hyperleukocytosis in chronic myeloid leukemia by leukapheresis: a case report**

*Logesvaran Murugan, Aida Zairani Mohd Zahidin, Wan Haslina Wan Abdul Halim*

Issue 1-1, 2019

**5. The right eye abducens nerve palsy as a cranial neuropathy of dengue fever: the benefit of corticosteroids in an unusual dengue sequela**

*Mohd Khairul Bin Abd Majid, Umi Kalthum Md Noh, Safinaz Md Khialdin*

Issue 1-2, 2019

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*Original article*
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# Combination of half-dose photodynamic therapy and anti-VEGF versus anti-VEGF monotherapy for polypoidal choroidal vasculopathy

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## Abstract

*Introduction*: Polypoidal choroidal vasculopathy (PCV) is an abnormality of the inner choroidal vasculature. The recommended treatment for PCV is a combination of standard verteporfin photodynamic therapy (PDT) with intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF). There have been reports of success with combination of half-dose PDT (hd-PDT) and anti-VEGF in the treatment of PCV. hd-PDT might be a cost-effective method with favourable outcome in the treatment of PCV and fewer side effects.
*Purpose*: To explore the efficacy of hd-PDT combined with anti-VEGF and anti-VEGF monotherapy in PCV.
*Study design:* Retrospective nonrandomized comparative study.
*Material and methods*: We conducted a retrospective nonrandomized comparative records review of all patients with PCV received a combination of hd-PDT and anti-VEGF *vs* anti-VEGF monotherapy from November 2017 to November 2019 at

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Hospital Tengku Ampuan Afzan, Pahang, Malaysia. Patients received a half-dose of verteporfin over 10 minutes and were irradiated by the standard fluence combined with intravitreal ranibizumab or aflibercept injections. The monotherapy group received either intravitreal ranibizumab or aflibercept. Primary outcome measures were best-corrected visual acuity (BCVA) and central subfield thickness (CST) at 6 months post-treatment. Secondary outcome measure was documentation of side effects.
*Results:* The study included a total of 16 patients, with 8 patients (8 eyes) in the combination group and 8 patients (10 eyes) in the monotherapy group. At 6 months post-treatment, the BCVA changes in logarithm of the minimum angle of resolution (logMAR) were -0.06 in the combination group and +0.02 in the monotherapy group ($p$ = 0.928). The average CST reduction was 51.6 µm in the combination group and 106.1 µm in the monotherapy group ($p$ = 0.214). One eye developed subretinal haemorrhage after hd-PDT and one eye developed retinal atrophy in the monotherapy group.
*Conclusion:* hd-PDT combined with anti-VEGF was able to produce similar functional outcomes in terms of BCVA when compared to anti-VEGF monotherapy. However, monotherapy is shown to be superior to combination treatment for anatomical improvement.

*Keywords:* anti-vascular endothelial growth factor, half-dose photodynamic therapy, polypoidal choroidal vasculopathy, verteporfin

# Abstrak

*Pengenalan:* Vaskulopati koroidal polypoidal ('polypoidal choroidal vasculopathy'(PCV)) adalah melibatkan keabnormalan pada lapisan dalam jaringan salur darah koroidal. Rawatan lazim yang disyorkan untuk PCV adalah kombinasi terapi fotodinamik verteporfin (photodynamic therapy (PDT)) dengan suntikan faktor pertumbuhan endothelial anti-vaskular (anti-VEGF) ke dalam mata. Terdapat kajian tentang kejayaan kombinasi PDT separuh dos (hd-PDT) dan anti-VEGF dalam rawatan PCV. hd-PDT mungkin satu kaedah yang menjimatkan kos tetapi pada masa yang sama berkesan dalam rawatan PCV dengan sampingan yang minimum.
*Tujuan:* Untuk meneroka keberkesanan kombinasi hd-PDT dan anti-VEGF dengan monoterapi anti-VEGF dalam PCV rawatan.
*Reka bentuk kajian:* Kajian perbandingan retrospektif tanpa rawak
*Kaedah kajian:* Satu tinjauan rekod retrospektif terhadap semua pesakit PCV yang menerima kombinasi hd-PDT dan anti-VEGF berbanding dengan monoterapi anti-VEGF dari November 2017 hingga November 2019 di Hospital Tengku Ampuan Afzan, Pahang, Malaysia. Pesakit menerima verteporfin separuh dos selama 10

minit dan disinari oleh kelancaran piawai yang digabungkan dengan suntikan intravitreal ranibizumab atau aflibercept. Kumpulan monoterapi adalah pesakit yang menerima ranibizumab intravitreal atau aflibercept sahaja. Hasil utama kajian adalah penglihatan (BCVA) dan ketebalan pusat tengah (CST) pada 6 bulan selepas rawatan. Kesan sampingan juga didokumentasi.
*Hasil kajian:* Kajian ini merangkumi sejumlah 16 pesakit, dengan 8 pesakit (8 mata) dalam kumpulan kombinasi dan 8 pesakit (10 mata) dalam kumpulan monoterapi. Pada 6 bulan selepas rawatan, perubahan BCVA dalam logMAR adalah -0.06 pada kumpulan kombinasi dan +0.02 pada kumpulan monoterapi ($p$ = 0.928). Pengurangan CST purata ialah 51.6 µm pada kumpulan kombinasi dan 106.1 µm pada kumpulan monoterapi ($p$ = 0.214). Satu mata mengalami pendarahan subretinal selepas hd-PDT manakala satu mata mengalami penipisan saraf mata pada kumpulan monoterapi.
*Kesimpulan:* Kombinasi hd-PDT dengan anti-VEGF memberi kesan yang sama dengan monoterapi anti-VEGF dari segi penglihtan. Manakala, rawatan monoterapi memberi pemulihan anatomi yang lebih berkesan daripada rawatan kombinasi.

*Kata kekunci:* faktor pertumbuhan endothelial anti-vaskular, polypoidal choroidal vasculopathy, terapi fotodinamik verteporfin yang separuh dos, verteporfin

## Introduction

Polypoidal choroidal vasculopathy (PCV) is an abnormality of the inner choroidal vasculature. It is a subtype of neovascular age-related macular degeneration (nAMD), and typically affects darker-skinned ethnicities such as Asians and African Americans. It is characterized by serosanguinous pigmented epithelium detachments and exudative changes leading to subretinal fibrosis and haemorrhage in multiple retinal layers.[1] PCV may be underdiagnosed in people who are not Asian, as indocyanine green angiography (ICGA) is not routinely performed in non-Asian countries.

There are various treatment options for PCV, including photodynamic therapy (PDT), anti-vascular endothelial growth factor (VEGF) monotherapy, and combination therapy. PDT with verteporfin (vPDT) is the first widely used treatment for PCV and it helps in polyp regression.[2] Standard PDT is the energy delivery dose of 50 J/cm$^2$, irradiance of 600 mW/cm2 of 689 nm light over 83 seconds with a verteporfin dose of 6 mg/m$^2$. In the era of anti-VEGF, many studies such as ANCHOR, MARINA, and VIEW 1 and VIEW 2 have shown that intravitreal ranibizumab or aflibercept injections are the standard treatment for nAMD.[3-5] Based on the PLANET study, aflibercept with sham vPDT is noninferior to aflibercept with rescue vPDT at 52 weeks in PCV treatment.[6] The LAPTOP study from Japan showed ranibizumab to be more effective than PDT for treatment-naïve PCV.[7] In EVEREST I and II, combination therapy of

vPDT and ranibizumab was shown to be superior to ranibizumab monotherapy in terms of best-corrected visual acuity (BCVA), complete polyp regression, and number of anti-VEGF injections required in a year.[8,9] Much evidence supports that PDT and anti-VEGF treatment are effective in treating symptomatic patients with PCV to the point of complete regression and without severe vision loss. However, vPDT carries risks of recurrent haemorrhages, exudation, choroidal ischemia, and retinal atrophy.[10]

Various 'safety-enhanced' vPDT protocols have been revised to optimise treatment outcomes and reduce its side effects, typically using half-dose verteporfin (verteporfin 3 mg/m$^2$) or half-fluence vPDT (laser fluence 25 J/cm$^2$). Wong *et al.* has shown that half-dose PDT can lead to polyp regression and produces similar results as standard PDT.[11,12] Meanwhile, several studies have demonstrated reduced fluence PDT was able to control the disease successfully.[13,14] In a study Nicolo *et al.*, hd-PDT was found to be more effective than half-fluence PDT for central serous chorioretinopathy.[15] A study by William *et al.* found that intravitreal ranibizumab monotherapy and combination of half-fluence PDT with ranibizumab in the treatment of nAMD appeared to have similar efficacy.[16] However, there were no studies looking into the outcome between combination of hd-PDT with anti-VEGF injection and anti-VEGF injection alone in the treatment of PCV. Thus, this study was conducted to compare the outcomes between hd-PDT combined with anti-VEGF and anti-VEGF monotherapy.

## Material and methods

This is a retrospective, nonrandomized, comparative review of the medical records of PCV patients who received combination of hd-PDT and anti-VEGF or anti-VEGF monotherapy from November 2017 to November 2019 at Hospital Tengku Ampuan Afzan, Pahang, Malaysia. This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia with the National Medical Research Register number (NMRR-20-609-54356).

A diagnosis of PCV was confirmed by indocyanine green angiography (ICGA) with the Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany) based on the EVEREST trial[17] or optical coherence tomography (OCT) suggestive of PCV features. Patients who received treatment previously with vPDT, pneumatic displacement of submacular haemorrhage, or focal laser photocoagulation were excluded, as well as patients who had other macular pathologies such as myopic maculopathy, retinal detachment, and macular hole.

Patients received half the standard dose of 3 mg/m$^2$ verteporfin (Visudyne; Novartis Pharma AG, Basel, Switzerland) over 10 minutes and were irradiated by the standard fluence (50 J/cm2, 83 s, 600 mW/cm2 at 689 nm) combined with three loading doses of either intravitreal ranibizumab (0.5 mg/0.05 ml, Lucentis; Novartis

Pharma AG, Basel, Switzerland) or intravitreal aflibercept (2 mg/0.05 ml, Eylea; Bayer, Leverkusen, Germany). The laser spot size was added 1,000 mm to the entire PCV lesion, including any polyps and branching vascular networks (BVN) as seen on ICGA. This included the subfoveal area for some patients. Another group of patients received either intravitreal ranibizumab or aflibercept. For the monotherapy group, they were given three loading doses of anti-VEGF followed by "pro re nata" (PRN) regimen depending on disease activity such as visual acuity, OCT changes, or new symptoms. Patients were examined at baseline and followed up until 6 months after treatment. Primary outcome measures were changes in BCVA and central subfield thickness (CST) by OCT (Spectral Domain Cirrus OCT Model 4000, Carl Zeiss Meditech, Jena, Germany) at 6 months post-treatment. Secondary outcome measure was documentation of side effects. The number of re-treatments with either hd-PDT or intravitreal anti-VEGF injection during these 6 months were also evaluated.

## Results

A total of 20 eyes of 18 patients were diagnosed as PCV and treated either with combination of hd-PDT and anti-VEGF or anti-VEGF alone. Eight patients underwent combination therapy while 10 patients were in the anti-VEGF monotherapy group. However, among the 10 patients in the monotherapy group, two patients were excluded as one patient defaulted follow-up and we were unable to obtain a clear image on OCT due to breakthrough vitreous haemorrhage in another patient. Thus, we studied the medical records from these 16 patients (18 eyes), with 8 patients (8 eyes) in the combination group and 8 patients (10 eyes) in the monotherapy group.

Mean age was 70 years in the combination group and 69.7 years in the monotherapy group; there were an equal number of males and females in each group. The proportion of left eyes was greater than right eyes, with a ratio of 2:6 in the hd-PDT group and 4:6 in the anti-VEGF group. The number of treatment-naïve patients were three in the hd-PDT group and seven in monotherapy group. Other patients had a history of previous anti-VEGF treatment. The mean number of previous anti-VEGF treatments was 4.1 ± 3.9 ranibizumab injections (range, 0–10 injections) and 0.3 ± 0.7 aflibercept injections (range, 0–2 injections) in the hd-PDT group, while in the anti-VEGF monotherapy group it was 0.9 ± 1.5 ranibizumab injections (range, 0–4 injections) and 0.4 ± 0.8 aflibercept injections (range, 0–2 injections). Five patients from the combination hd-PDT and anti-VEGF group had BVN, whereas none of the patients in the monotherapy group had BVN at presentation. There were two patients with subfoveal polyp, five patients with juxtafoveal polyp, and one patient with extrafoveal polyp. Mean vision logMAR at baseline was 1.27 ± 0.72 in the hd-PDT group and 0.98 ± 0.61 in the monotherapy group. The pre-treatment CST mean from OCT was 307.4 ± 85.2 μm in the combination group and

*Table 1.* Demographic data and clinical parameters

| **Parameters** | **hd-PDT + anti-VEGF** | **Anti-VEGF** | ***P*** |
|---|---|---|---|
| Number of patients (eyes) | 8 (8) | 8 (10) | |
| Average age | 70 | 69.7 | 0.755[a] |
| Male:female | 4:4 | 4:4 | 0.664[b] |
| Laterality (right:left) | 2:6 | 4:6 | 0.638[b] |
| BVN | 5 | 0 | 0.007[b] |
| No previous treatment | 3 | 7 | 0.342[b] |
| Previous anti-VEGF injection<br>- Ranibizumab (range)<br>- Aflibercept (range) | 4.4 ± 4.2<br>4.1 ± 3.9 (0–10)<br>0.3 ± 0.7 (0–2) | 1.3 ± 2.2<br>0.8 ± 1.5 (0–4)<br>0.4 ± 0.8 (0–2) | 0.087[a]<br>0.051[a]<br>0.680[a] |
| logMAR BCVA<br>at baseline (Snellen line) | 1.27 ± 0.7 (20/372) | 0.98 ± 0.6 (20/190) | 0.500[a] |
| CST at baseline (μm) | 307.4 ± 85.2 | 387.3 ± 118.5 | 0.131[a] |

hd-PDT: half-dose photodynamic therapy; anti-VEGF: anti-vascular endothelial growth factor; BVN: branching vascular network; BCVA: best-corrected visual acuity; CST: central subfield thickness
[a]Mann-Whitney U test
[b]Fisher's exact test

387.3 ± 118.5 μm in the monotherapy group. Except the number of patients with BVN, there were no statistically significant differences in parameters between the two groups (Table 1).

At 6-months post-treatment, the mean of intravitreal anti-VEGF injections received in the combination group was 3.3 ± 0.9 for ranibizumab and 0.6 ± 1.1 for aflibercept, and 2.7 ± 1.8 for ranibizumab and 0.8 ± 1.0 for aflibercept in the monotherapy group. No hd-PDT was repeated in these 6 months. The mean CST reduced to 255.8 ± 76.3 μm (51.6 μm reduction) in the combination group and 284.9 ± 135.1 μm (102.4μm reduction) in the monotherapy group. There was greater CST reduction from baseline in the monotherapy group than in the hd-PDT group, but this did not reach statistical significance. Two eyes in the combination group had complete resolution of fluid on OCT, while three eyes had complete resolution of fluid in the monotherapy group. BCVA measured in logMAR after 6 months post-treatment was 1.21 ± 0.73 (logMAR 0.06 improvement) in the hd-PDT + anti-VEGF group and 1.00 ± 0.60 (logMAR 0.02 deterioration) in the monotherapy group. The combination group showed slightly better visual outcome than monotherapy. The differences in anatomical and functional outcomes between both groups were not statistically significant, as shown in Table 2.

*Table 2.* Anatomical and functional outcomes at 6 months post-treatment

| **Parameters** | **hd-PDT + anti-VEGF (*n* = 8 eyes)** | **Anti-VEGF (*n* = 10 eyes)** | ***P*** |
|---|---|---|---|
| Intravitreal anti-VEGF<br>- Ranibizumab<br>- Aflibercept | 3.9 ± 1.0<br>3.3 ± 0.9<br>0.6 ± 1.1 | 3.5 ± 1.4<br>2.7 ± 1.8<br>0.8 ± 1.0 | 0.640[a]<br>0.582[a]<br>0.760[a] |
| LogMAR BCVA (Snellen line) | 1.21 ± 0.73 (20/324) | 1.00 ± 0.60 (20/200) | 0.391[a] |
| LogMAR BCVA changes (logMAR letter) | -0.06 (3-letter improvement) | +0.02 (1-letter deterioration) | 0.928[a] |
| CST, µm | 255.8 ± 76.3 | 294.9 ± 135.1 | 0.594[a] |
| CST reduction, µm | 51.6 | 92.4 | 0.214[a] |
| Eyes with complete fluid resorption (%) | 2 (25%) | 3 (30%) | 1.000[b] |

hd-PDT: half-dose photodynamic therapy; anti-VEGF: anti-vascular endothelial growth factor; BVN: branching vascular network; BCVA: best-corrected visual acuity; CST: central subfield thickness
[a]Mann-Whitney U test
[b]Fisher's exact test

In the hd-PDT group, subretinal haemorrhage occurred in one eye (12.5%). One eye (10%) developed retinal atrophy in the anti-VEGF monotherapy group. No other complications were documented.

## Discussion

Combination of standard PDT with anti-VEGF has been the established strategy for treating PCV provided no contraindication to PDT. Verteporfin is a photoactivated dye that binds to low-density lipoproteins (LDL) and becomes concentrated in the proliferating vascular bed of the neovascular choroid, in which there is increased expression of LDL receptors. Verteporfin is stimulated by the laser energy, causing the release of free radicals and leading to local endothelial cell damage and occlusion of the blood supply to the abnormal vascularisation without significant damage the other normal vessels.[18] PDT is proven to induce regression of polyps; anti-VEGF is important to allow fluid absorption from the retina and control VEGF upregulation. Therefore, the combination of PDT and anti-VEGF has a synergistic effect on visual and anatomical outcome.

However, multiple complications of standard PDT have been reported in many studies, including choroidal ischaemia, retinal pigment epithelium atrophy, persistent recurrent exudation, secondary choroidal neovascularisation, and fibrosis that cause poor vision despite PCV regression.[19] In the TAP and VIP studies, the incidence of vPDT treatment-related serious adverse events was 3.8%.[20, 21] Thus, several studies showed favourable outcomes with combination of reduced fluence PDT and ranibizumab injection treatment in PCV cases while minimizing the standard PDT side effects.[13, 22] The alternative way to reduce PDT complications is by reducing the verteporfin dose. hd-PDT is also considered to have fewer side effects[23] while also inducing fluid resorption faster and having a more lasting effect than half-fluence PDT in treating central serous chorioretinopathy (CSCR).[15] hd-PDT can be considered to treat PCV, as both CSCR and PCV share a similar pathogenesis, which is the hyperpermeability of the underlying choroid. Ian *et al.* found that hd-PDT combined with intravitreal ranibizumab can cause greater polyp regression in PCV with a single polyp[11] and was able to produce similar results to standard-PDT at 1 year.[12] In their retrospective study, Lee *et al.* showed that hd-PDT caused less damage to the physiologic choroid; however, the complete polyp regression rate at 3 months was lower than for full-dose PDT (43.3% *versus* 72.7%).[24]

In our study, BCVA at 6 months improved slightly on combination of hd-PDT and anti-VEGF and deteriorated slightly on anti-VEGF monotherapy. BCVA improvement (logMAR 0.06) was superior in the combination group compared to the monotherapy group, although the improvement was statistically not significant. This result is better than reported in Ian *et al.*, which showed 0.01 logMAR improvement in the hd-PDT group and 0.03 logMAR improvement in the standard PDT group.[12] For CST, at 6 months post-treatment both groups had improved, but the monotherapy group showed greater CST reduction, which is similar to the results found by Ian *et al.* Only 20% of eyes in the combination group had complete fluid resorption whereas 30% of the monotherapy group achieved complete fluid resorption. The possible explanation for this result was due to the influence of BVN. Five eyes with BVN were detected in our combination group, while there were none in the monotherapy group. BVN has been reported as more resistant to either PDT or anti-VEGF and is the source of recurrent active leaking polyps.[25] Our results were different from previous studies using half fluence PDT, as our combination group had five eyes (62.5%) with BNV and none with BNV in the monotherapy group. Furthermore, the combination group had only three treatment-naïve eyes (37.5%), with the remaining 5 eyes (62.5%) treated with at least four prior anti-VEGF injections, whereas the monotherapy group had seven treatment-naïve eyes (70%). As a result, patients in the monotherapy group likely had shorter presentation and received treatment earlier than the combination group. Both groups received a similar number of ranibizumab and aflibercept injections for 6 months. In the subanalysis for treatment-naïve patients in both groups, BCVA in the combination group improved significantly (logMAR 0.23 improvement), while the monotherapy group only had a 0.06

logMAR improvement. However, CST reduction was greater in the monotherapy group than in the combination group with 34.4 µm and 83.2 µm, respectively.

There were no serious side effects documented among these cases. Only one eye (12.5%) has subretinal haemorrhage after hd-PDT and one eye (10%) developed retinal atrophy in the anti-VEGF monotherapy group. This complication percentage in the combination group is lower compared to standard PDT treatment, where an estimated 30% of patients suffer ocular adverse effects.[9,26]

The limitations of our study include its retrospective, nonrandomized nature, small sample size, short duration of 6 months, heterogeneity of anti-VEGF agents and PCV lesion types, and lack of repeated ICGA at the end of 6 months to assess polyp closure. Additionally, combination therapy tends to be used in patients with BNV or previously failed monotherapy treatment, leading to selection bias. This reflects treatment in the real-world setting. Further prospective, randomized studies with larger sample sizes, longer duration, and standardization of anti-VEGF agents are required to investigate the long-term efficacy and safety of combination hd-PDT treatment compared to single-agent anti-VEGF monotherapy, as well as to identify suitable lesion types for combination therapy.

hd-PDT combined with anti-VEGF was able to produce similar functional outcomes in terms of BCVA when compared to anti-VEGF monotherapy. However, monotherapy has shown to be superior to combination treatment for anatomical improvement but not statistical significance. In conclusion, hd-PDT is a safe and effective treatment for PCV.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia with the National Medical Research Register number (NMRR-20-609-54356).

**Competing interests**
None to declare.

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# Diagnostic accuracy of total macular and ganglion cell layer thickness in differentiating different stages of glaucoma: an SD-OCT study

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## Abstract

*Purpose:* To determine the diagnostic accuracy of mean macular retinal thickness (mRT) and macular ganglion cell layer (mGCL) thickness measured by Spectralis spectral-domain optical coherence tomography (SD-OCT) posterior pole thickness map (PPTM) in differentiating between normal and glaucoma eyes of different severity.
*Study design:* Cross-sectional study.
*Methods:* All subjects were divided into normal and glaucoma groups according to the visual fields-based Glaucoma Staging System. They underwent slit-lamp examination, Humphrey visual field test, and SD-OCT (PPTM) imaging. mRT and mGCL thickness measurements were recorded. Analysis of variance with the least significant difference *post hoc* test was used for pairwise comparison. Ability to discriminate between normal eyes and those with differing severity of glaucoma was assessed using the area under the receiver operating characteristic curve (AUROC).
*Results:* A total of 201 eyes from 201 subjects were enrolled in this study. The mean mRT in the normal population, mild-moderate glaucoma, and advanced-severe

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glaucoma was 290.2 ±12.1μm, 270.1 ± 17.0 μm, and 259.1 ± 15.0 μm, respectively. Mean mGCL thickness for the corresponding three groups was 32.3 ± 2.8 μm, 27.6 ± 3.3 μm and 22.2 ± 3.8μm, respectively. AUROC analysis showed excellent diagnostic discrimination between glaucoma and normal subjects for mRT (AUC: 0.90) and mGCL thickness (AUC: 0.92). The cut-off value of mRT was 274.9 μm (90% sensitivity, 75% specificity) and of mGCL thickness was 27.9 μm (93% sensitivity, 74% specificity). The discrimination ability performance of mRT and mGCL thickness deteriorated with increasing severity of glaucoma with mGCL thickness (AUC: 0.67–0.87) performing slightly better than mRT for all grades (AUC: 0.58–0.71). *Conclusions:* mRT and mGCL thickness measurement on PPTM showed great sensitivity and specificity to discern between normal and glaucomatous subjects. The discrimination ability of mRT and mGCL thickness, however, decreases with increasing grade of glaucoma. We believe SD-OCT PPTM offers an alternative imaging method to detect early glaucoma.

*Keywords:* glaucoma, glaucoma grading system, macular ganglion cell layer (mGCL), macular retinal thickness (mRT), spectral domain optical coherence tomography (SD-OCT)

# Abstrak

*Tujuan:* Untuk menentukan ketepatan diagnostik di antara pesakit glaukoma dan normal (bukan glaukoma) berdasarkan purata ketebalan macular retina macular ("macular retinal thickness" [mRT]) dan lapisan sel ganglion makular ("macular ganglion cell layer" [mGCL)]) yang diukur oleh tomografi optikal koheren spektral domain ("spectral-domain optical coherence tomography" [SD-OCT]) (Spectralis) pada peta ketabalan polar posterior ("Posterior Pole Thickness Map" [PPTM]).
Reka betuk kajian: Kajian keratan rentas.
*Kaedah kajian:* Subjek dibahagikan kepada dua kumpulan: glaukoma dan normal berdasarkan skor ke atas medan penglihatan mengikut sistem tahap glaukoma ("Glaucoma Staging System" [GSS]).

Kesemua subjek telah menjalani pemeriksaan slitlamp, ujian medan penglihatan (Humphrey), dan pengimejan tomografi SD-OCT (PPTM). Ukuran mRT dan mGCL dibuat dan direkodkan. Perbandingan secara berpasangan dibuat menggunakan ujian analisa varians dengan perbezaan yang paling ketara secara post-hoc. Keupayaan untuk mendiskriminasi antara normal dan pelbagai tahap keterukkan glaukoma diuji dengan ujian statistik menentukan Kawasan dibawah lengkung karakter operasi penerima ("area under the receiver operating characteristic curve" [AUROC]).
*Keputusan:* Kajian ini melibatkan 201 mata daripada 201 subjek. Purata mRT dalam kumpulan normal dan kumpulan glaukoma secara berpasangan tahap keterukan

ringan-sederhana dan teruk adalah 290.2 ± 12.1μm, 270.1 ± 17.0 μm dan 259.1 ± 15.0 μm. Purata ketebalan mGCL untuk tiga kumpulan yang sepadan adalah 32.3 ± 2.8μm, 27.6 ± 3.3 μm dan 22.2 ± 3.8 μm. Analisa AUROC menunjukkan diskriminasi diagnostik yang sangat baik untuk glaukoma dan subjek biasa untuk mRT (AUC: 0.90) dan ketebalan mGCL (AUC:0.92). Penetapan nilai mRT adalah 274.9 μm (pada tahap 90% sensitiviti, 75% spesifikasi) dan ketebalan mGCL adalah 27.9μm (93% sensitiviti, 74% spesifikasi). Keupayaan diskriminator mRT dan ketebalan mGCL merosot dengan peningkatan tahap keterukan glaucoma. Manakala purata ketebalan mGCL (AUC: 0.67–0.87) menunjukkan keupayaan diskriminator lebih baik daripada purata mRT (AUC: 0.58–0.71) untuk semua tahap keterukkan glaucoma.

*Kesimpulan:* Pengukuran ketebalan mRT dan mGCL dengan PPTM menunjukkan sensitiviti dan spesifikasi yang tinggi dalam membezakan antara glaukoma dan bukan glaukoma. Keupayaan diskriminator mRT dan ketebalan mGCL, bagaimanapun, berkurangan dengan peningkatan keterukkan glaukoma. SD-OCT PPTM menawarkan kaedah pengimejan alternatif untuk mengesan glaukoma pada peringkat awal.

*Kata kekunci:* glaukoma, ketebalan retinal makular, lapisan sel ganglion makular, sistem penggredan glaukoma, spectral-domain optical coherence tomography

## Introduction

Glaucoma is a complex multi-factorial disorder characterised by progressive loss of retinal ganglion cell, axons, nerve fibre layer, and visual field loss.[1] Macular thickness is correspondingly reduced in glaucomatous eyes with the ganglion cell layer particularly affected.[2] Previous studies have been done to determine macular thickness in glaucoma patients using the modified Early Treatment of Diabetic Retinopathy Study macular map.[3-6] However, with the spectral-domain optical coherence tomography (SD-OCT) posterior pole thickness map (PPTM) available from Spectralis (Heidelberg Engineering, Carlsbad, CA, USA), a larger area of the macula is captured, enabling assessment of changes in the glaucoma disease process.

The Early Treatment of Diabetic Retinopathy Study macular map only covers a small area (6 mm) of the macula, centred around the fovea, which is equivalent to a 10° visual field test.[3-7] The PPTM covers a larger area (9 mm) of the macula and is comparable with the central 4 X 4 points among the 52 test points of the 24-2 visual field test.[8,9] The colour scale of the PPTM is finer than the existing Early Treatment of Diabetic Retinopathy Study macular map and is sensitive to change in thickness as small as 1 μm.[10] Theoretically, the PPTM will perform better in diagnosing glaucoma based on macular thickness, as the projection of retinal ganglion cell

axons follows the horizontal raphe and scanning larger macular areas theoretically provide more practical information.[11] Isolation of the ganglion cell layer should enhance the diagnostic power of the macular imaging as it gets rid of the disparity caused by the outer retinal layers.[4]

This study was conducted to determine the diagnostic accuracy of the total macular and ganglion cell layer thickness measured by PPTM using SD-OCT in differentiating between normal eyes and those with different severity of glaucoma.

## Methods

This was a cross-sectional study conducted from May 2018 to May 2019. Ethical approval was obtained prior to the commencement of the study from the Medical Research & Ethics Committee (NMRR-18-458-39979). Informed consent was obtained from all participants. It was conducted in accordance with the Declaration of Helsinki.

All subjects underwent thorough ophthalmic examination, including best-corrected visual acuity (BCVA), slit-lamp examination, intraocular pressure measurement using Goldmann applanation tonometry, dilated fundus, and optic disc assessment. Visual field test was performed using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) with the central 24-2 pattern of the Swedish Interactive Threshold Algorithm standard strategy. The visual field results were considered reliable when false-positive and negative errors were < 33% and fixation losses were < 20%.[8] One eye from each subject was randomly selected if both eyes were eligible.

The eligible eyes were categorized into normal or different severity of glaucoma. All normal subjects had to fulfil the following inclusion criteria: age above 20 years, no history of glaucoma in the family or chronic corticosteroid use, BCVA ≥ 6/12, no abnormality on ocular examination, intraocular pressure ≤ 21 mmHg, normal optic nerve head appearance, and normal 24-2 Swedish Interactive Threshold Algorithm-standard Humphrey visual field test (mean deviation and pattern standard deviation within 95% confidence limits, with fewer than three non-edge contiguous points within the same hemifield identified as significant ($P$ <0.05) in the pattern deviation plot, and glaucoma hemifield test results within normal limits).[4]

The glaucoma subjects were divided into four subgroups: mild (mean deviation better than -6.00 dB), moderate (mean deviation -6.01 dB to -12.00 dB), advanced (mean deviation -12.01 dB to -20.00 dB), and severe (mean deviation -20.01 dB or worse) according to the visual field-based Glaucoma Staging System (Stages 1–4 of the Bascom Palmer [Hodapp-Anderson-Parrish] Glaucoma Staging System).[12] All glaucoma subjects had to fulfil the following inclusion criteria: glaucomatous appearance of the optic disc.[13] and retinal nerve fibre layer defect corresponding with typical reproducible visual field defects. All glaucoma subjects had confirmed

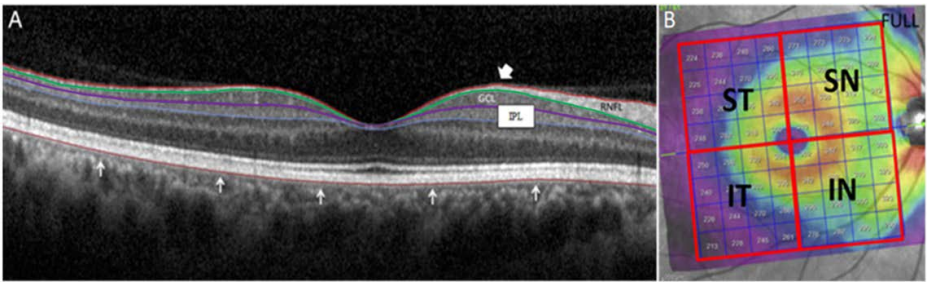



*Fig. 1.* (*A*) Segmentation of the retinal layers with Glaucoma Premium Module Edition software on a normal subject. Macular retinal thickness (mRT) is between the white block arrowhead and white arrows. White block arrowhead: inner limiting membrane; white arrows: outer border of the retinal pigment epithelium. Macular ganglion cell layer (mGCL) is the hyporeflective layer between the green and purple lines. Green line: outer border of the retinal nerve fibre layer (RNFL); purple line: outer border of the inner plexiform layer (IPL). (*B*) Color-coded map of PPTM, 8 x 8 grid centred on the foveal pit and aligned to the fovea-disc axis. Posterior pole is divided into quadrants. ST: superior temporal; SN: superior nasal; IT: inferior temporal; IN: inferior nasal.

diagnosis for more 6 six months and performed at least three previous reliable visual fields. All patients with open- and closed-angle primary glaucoma were included.

Exclusion criteria for all groups were: coexisting ocular or systemic disease that could cause visual field loss; disability, mental or other, that could prevent the correct understanding of the information needed for informed consent; refractive error of more than ± 3 dioptres (D); media opacities; and any pathology or prior procedures that could affect macular thickness such as diabetic retinopathy, macular degeneration, epiretinal membrane, previous ocular surgery for macular disorder, and retinal laser procedures. Subjects with unreliable visual fields were also excluded.

All the subjects underwent retinal imaging with the Spectralis SD-OCT using the Glaucoma Module Premium Edition software on the same day as the visual field test to obtain the macular retinal thickness (mRT) and macular ganglion cell layer (mGCL) thickness. SD-OCT images were acquired in a dark room by the same experienced operator on dilated pupil using image alignment eye-tracking software (TruTrack; Heidelberg Engineering); an internal fixation target was used to provide the highest reproducibility of the images. Through the automated real-time function of the SD-OCT device, each B-scan was repeated nine to eleven times to improve the quality of the images.[10] PPTM can measure the macular thickness at the central 20° of the posterior pole (9 mm) using 61 horizontal B-scans (30° X 25° OCT volume scan). Segmentation of the retinal layers was performed automatically by the Spectralis SD-OCT software.[9, 14] The quality of the scans was assessed and scans with a quality score of less than 25 dB, any visible motion or blinking artifacts, and any detected macular pathology were rejected.

The PPTM displays the retinal thickness in the respective cell of the grid. Mean mRT and mGCL thickness were calculated automatically and further divided into mean thickness at the superior and inferior hemispheres. Data of retinal thickness values in each square cell of the total 64 square cells were collected and the mean was calculated based on different quadrants of posterior pole (Fig. 1).

**Statistical analysis**

The normality of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were analysed using either the Kruskal-Wallis or Chi-square test. Analysis of variance with the least significant difference *post hoc* test was used for pairwise comparison. The diagnostic capabilities and accuracy of each variable to differentiate between normal and glaucoma eyes of different severity were determined by calculating the area under the receiver operating characteristic curve (AUROC). The receiver operating characteristic curve shows the trade-off between sensitivity and specificity. Statistical analysis was performed using Statistical Package for the Social Sciences version 21.0 (IBM, USA). A *P*-value of < 0.05 was considered as statistically significant.

## Results

During the study period, 218 subjects underwent a comprehensive examination and satisfied the inclusion and exclusion criteria in the study. Seventeen eyes were excluded due to poor image quality on OCT ($n = 8$), non-clinically detectable small serous pigment epithelial detachment ($n = 2$), presence of minor retinal pigment epithelial irregularities ($n = 4$), and epiretinal membrane ($n = 3$). This left a remainder of 201 eyes, which was almost equally divided among the five groups. The demographic and clinical characteristics of the normal and glaucoma groups are shown in Table 1. The glaucomatous eyes in this study included 126 eyes (78.3%) with open-angle glaucoma and 35 eyes (21.7%) with angle-closure glaucoma. Open-angle glaucoma groups included patients with primary open-angle glaucoma (82.2%) and normal-tension glaucoma (17.8%). All subjects in the angle-closure glaucoma group were primary angle-closure glaucoma and the majority of subjects (82.3%) were chronic angle-closure glaucoma, while acute angle-closure glaucoma subjects accounted for 17.7%.

Mean mRT and mGCL thickness in the normal population and the different grades of glaucoma are shown in Figure 2. Decreasing thickness was noted with increasing severity of glaucoma. Mean mRT in the normal, mild-moderate, and advanced-severe glaucoma groups was 290.2 ± 12.1 µm, 270.1 ± 17.0 µm, and 259.1 ± 15.0 µm, respectively, while mean mGCL thickness was 32.3 ± 2.8 µm, 27.6 ± 3.3 µm, and 22.2 ± 3.8 µm, respectively. The difference between the groups was statistically significant ($P < 0.001$).

*Table 1.* Demographic and clinical characteristics of normal and glaucoma groups

| | Normal | Glaucoma (*n* = 161) | | | | *P*-value |
|---|---|---|---|---|---|---|
| | | Mild (*n* = 40) | Moderate (*n* = 41) | Advanced (*n* = 40) | Severe (*n* =40) | |
| **Age (years)** | 62.00 (54.25 – 70.00) | 65.85 (62.86 – 68.84) | 69.85 (67.62 – 72.08) | 64.10 (60.92 – 67.28) | 61.38 (56.62 – 66.23) | 0.112 [a] |
| **Male/ Female (*n*/*n*)** | 14/26 | 25/15 | 26/15 | 25/15 | 29/11 | 0.001 [b] |
| **IOP (mmHg)** | 17.1 ± 1.6 | 16.2 ± 3.2 | 15.1 ± 2.5 | 14.3 ± 1.2 | 15.3 ± 1.1 | 0.330 [a] |
| **VF MD (dB)** | -1.20 (-2.26 ± 1.55) | -2.76 (-3.79 – -1.87) | -6.17 (-8.38 – -5.16) | -14.05 (-16.39 – -11.98) | -23.42 (-26.70 – -21.62) | < 0.001 [a] |
| **VF PSD (dB)** | 1.55 ± 0.2 | 2.17 ± 0.4 | 5.30 ± 0.3 | 12.25 ± 0.1 | 13.45 ± 0.2 | < 0.001 [a] |
| **Refraction (D)** | -2.81 ± 1.58 | -1.65 ± 2.08 | -1.85 ± 0.55 | -2.05 ± 1.75 | -2.55 ± 1.55 | 0.820 [a] |

IOP: intraocular pressure; VF: visual field; MD: mean deviation; PSD: pattern standard deviation
[a]Kruskal-Wallis test
[b]Chi-square Test

In both the normal and glaucoma groups, mean mRT and mGCL thickness were highest at the superior nasal quadrant, followed by the inferior nasal, superior temporal, and inferior temporal quadrants. Overall, the superior hemisphere was thicker compared to the inferior hemisphere. There was a significant decrease in thickness from the normal group to the glaucoma groups in all quadrants (Table 2).

The receiver operating curve analysis showed excellent diagnostic discrimination for glaucoma and normal subjects for mean mRT (AUROC: 0.901) and mGCL thickness (AUROC: 0.929). Cut-off values of less than 274.9 µm for mean mRT and less than 27.9 µm for mGCL thickness were highly sensitive and specific for the diagnosis of glaucoma (Fig. 3).

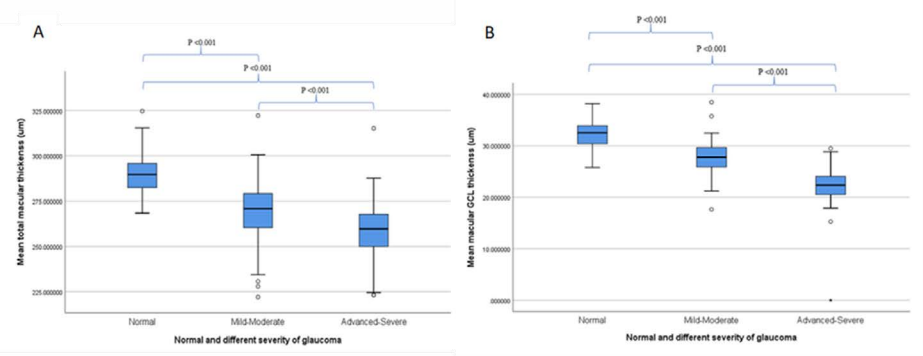



*Fig. 2.* Box-and-whisker plots showing the distribution of mean macular retinal thickness (*A*) and mean macular ganglion cell layer thickness (*B*) for normal and glaucoma eyes of different severity.

*Table 2.* Mean macular retinal thickness and macular ganglion cell layer thickness according to different quadrants of posterior pole in normal and different severity of glaucoma groups

| **Mean mRT** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Quadrant** | **Normal** | | **Mild-moderate glaucoma** | | **Advanced-severe glaucoma** | | ***P*-value*** |
| | **Mean ± SD (µm)** | **95% CI (µm)** | **Mean ± SD (µm)** | **95% CI (µm)** | **Mean ± SD (µm)** | **95% CI (µm)** | |
| **SN** | 310.1 ± 16.1†‡ | 304.9 – 315.2 | 292.3 ± 24.3†§ | 287.0 – 297.7 | 277.4 ± 17.6‡§ | 273.5 – 281.3 | < 0.001 |
| **IN** | 306.3 ± 17.1†‡ | 300.8 – 311.8 | 278.5 ± 26.0†§ | 272.7 – 284.2 | 263.2 ± 29.3‡§ | 256.7 – 269.8 | < 0.001 |
| **ST** | 273.4 ± 11.3†‡ | 269.8 – 277.0 | 259.5 ± 13.2†§ | 256.6 – 262.4 | 252.8 ± 13.1‡§ | 249.8 – 255.7 | < 0.001 |
| **IT** | 271.0 ± 10.7†‡ | 267.6 – 274.4 | 250.0 ± 22.2†§ | 245.1 – 254.9 | 243.2 ± 18.9‡§ | 239.0 – 247.4 | < 0.001 |
| **SH** | 291.7 ± 12.2†‡ | 287.8 – 295.6 | 275.90 ± 15.9†§ | 272.4 – 279.4 | 265.1 ± 14.4‡§ | 261.9 – 268.3 | < 0.001 |
| **IH** | 288.7 ± 12.5†‡ | 284.7 – 292.6 | 264.2 ± 23.4†§ | 259.1 – 269.4 | 253.2 ± 21.7‡§ | 248.4 – 258.0 | < 0.001 |

| Mean mGCL thickness | | | | | | | |
|---|---|---|---|---|---|---|---|
| Quadrant | Normal | | Mild-moderate glaucoma | | Advanced-severe glaucoma | | *P*-value* |
| | Mean ± SD (μm) | 95% CI (μm) | Mean ± SD (μm) | 95% CI (μm) | Mean ± SD (μm) | 95% CI (μm) | |
| SN | 33.4 ± 3.2†‡ | 32.4 – 34.4 | 29.6 ± 3.1†§ | 28.9 – 30.3 | 26.3 ± 5.1‡§ | 25.1 – 27.4 | < 0.001 |
| IN | 32.2 ± 3.2†‡ | 31.1 – 33.2 | 28.6 ± 4.1†§ | 27.7 – 29.4 | 23.8 ± 4.6‡§ | 22.8 – 24.8 | < 0.001 |
| ST | 31.7 ± 3.2†‡ | 30.7 – 32.7 | 26.5 ± 3.8†§ | 25.7 – 27.4 | 20.2 ± 4.4‡§ | 19.2 – 21.2 | < 0.001 |
| IT | 30.8 ± 2.9†‡ | 29.8 – 32.7 | 25.7 ± 4.6†§ | 24.7 – 26.7 | 18.7 ± 4.5‡§ | 17.7 – 19.7 | < 0.001 |
| SH | 32.6 ± 2.9†‡ | 31.6 – 33.5 | 28.1 ± 3.2†§ | 27.4 – 28.8 | 23.2 ± 4.4‡§ | 22.3 – 24.2 | < 0.001 |
| IH | 32.0 ± 2.8†‡ | 31.1 – 32.9 | 27.1 ± 4.0†§ | 26.3 – 28.0 | 21.3 ± 4.3‡§ | 20.3 – 22.2) | < 0.001 |

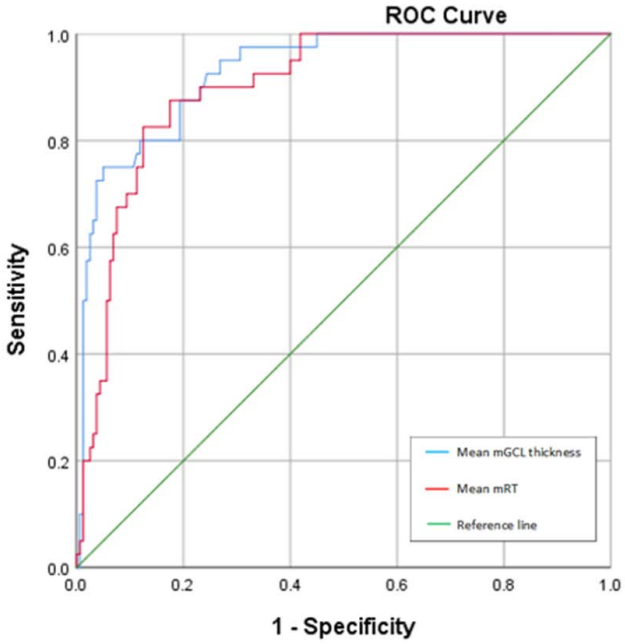
CI: confidence interval; IH: inferior hemisphere; IN: inferior nasal; IT: inferior temporal; mGCL: macular ganglion cell layer; mRT: macular retinal thickness; SD: standard deviation; SH: superior hemisphere; SN: superior nasal; ST: superior temporal

*$P$-values show significance of one-way ANOVA analyses.

†Significant ($P$ <0.05) in pairwise comparison (*post-hoc* LSD) of normal *vs* mild-moderate glaucoma.

‡Significant ($P$ <0.05) in pairwise comparison (*post-hoc* LSD) of normal *vs* advanced-severe glaucoma

§Significant ($P$<0.05) in pairwise comparison (*post-hoc* LSD) of mild-moderate *vs* advanced-severe glaucoma




| Parameters | Cut-off value | Sensitivity, % | Specificity, % | Glaucoma | | *P*-value |
|---|---|---|---|---|---|---|
| | | | | AUROC | 95% CI | |
| Mean mRT | <274.88 | 90 | 75 | 0.901 | 0.856 – 0.947 | <0.001 |
| Mean mGCL thickness | <27.94 | 93 | 74 | 0.929 | 0.890 – 0.968 | <0.001 |

*Fig. 3.* Receiver operating characteristic (ROC) curves and table showing the diagnostic capabilities and accuracy of mean mRT and mGCL thickness in differentiating glaucoma from normal subjects. mRT: macular retinal thickness; mGCL: macular ganglion cell layer; AUROC: area under the receiver operating characteristic; CI: confidence interval.

*Table 3.* Diagnostic capabilities and accuracy of mean macular retinal thickness and macular ganglion cell layer thickness in differentiating different stages of glaucoma subjects

| Parameters | Glaucoma stage | Cut-off value (µm) | Sensitivity, % | Specificity, % | AUROC | 95% CI |
|---|---|---|---|---|---|---|
| **Mean mRT** | Mild | 274.9 | 90 | 55 | 0.710 | 0.630–0.791 |
| | Moderate | 266.5 | 78 | 51 | 0.649 | 0.529–0.769 |
| | Advanced | 260.4 | 66 | 50 | 0.596 | 0.471–0.720 |
| | Severe | 257.5 | 60 | 54 | 0.583 | 0.457–0.709 |
| **Mean mGCL thickness** | Mild | 28.9 | 88 | 53 | 0.878 | 0.824–0.932 |
| | Moderate | 26.7 | 80 | 46 | 0.679 | 0.562–0.797 |
| | Advanced | 23.5 | 81 | 60 | 0.768 | 0.665–0.871 |
| | Severe | 22.1 | 73 | 62 | 0.695 | 0.578–0.811 |

AUROC: area under the receiver operating characteristic; CI: confidence interval; mGCL: macular ganglion cell layer; mRT: macular retinal thickness

*Table 4.* Diagnostic capabilities and accuracy of mean macular retinal thickness and macular ganglion cell layer thickness in differentiating glaucoma from normal subjects according to different quadrants of the posterior pole

| | Quadrant | Cut-off value | Sensitivity (%) | Specificity (%) | Glaucoma | | *P*-value |
|---|---|---|---|---|---|---|---|
| | | | | | AUROC | 95% CI | |
| **Mean mRT** | **SN** | ≤ 293.91 | 90 | 71 | 0.866 | 0.805 – 0.927 | < 0.001 |
| | **IN** | ≤ 283.41 | 90 | 71 | 0.895 | 0.839 – 0.951 | < 0.001 |
| | **ST** | ≤ 258.75 | 90 | 62 | 0.856 | 0.798 – 0.913 | < 0.001 |
| | **IT** | ≤ 259.94 | 90 | 79 | 0.887 | 0.838 – 0.936 | < 0.001 |
| | **SH** | ≤ 277.63 | 90 | 71 | 0.875 | 0.823 – 0.926 | < 0.001 |
| | **IH** | ≤ 268.41 | 90 | 70 | 0.904 | 0.859 – 0.950 | < 0.001 |
| **Mean mGCL thickness** | **SN** | ≤ 29.09 | 90 | 58 | 0.857 | 0.793 – 0.921 | < 0.001 |
| | **IN** | ≤ 28.09 | 90 | 63 | 0.862 | 0.802 – 0.921 | < 0.001 |
| | **ST** | ≤ 28.03 | 90 | 81 | 0.930 | 0.887 – 0.973 | < 0.001 |
| | **IT** | ≤ 28.63 | 93 | 88 | 0.941 | 0.905 – 0.977 | < 0.001 |
| | **SH** | ≤ 28.55 | 93 | 73 | 0.917 | 0.872 – 0.963 | < 0.001 |
| | **IH** | ≤ 27.53 | 90 | 70 | 0.922 | 0.882 – 0.963 | < 0.001 |

AUROC: area under the receiver operating characteristic; CI: confidence interval; IH: inferior hemisphere; IN: inferior nasal; IT: inferior temporal; mGCL: macular ganglion cell layer; mRT: macular retinal thickness; SH: superior hemisphere; SN: superior nasal; ST: superior temporal

The discrimination ability of mean mRT and mGCL thickness deteriorated with increasing severity of glaucoma (Table 3). Mean mGCL thickness performed better than mRT overall. Both mRT and mGCL thickness showed higher sensitivity in diagnosing mild glaucoma compared to other groups of glaucoma (mRT AUROC: 0.71, mGCL AUROC: 0.87).

The diagnostic power of the PPTM in differentiating glaucoma from normal subjects was greater in quadrant analysis. In particular, the inferior hemisphere quadrant for mean mRT (AUROC: 0.90, 95%, confidence interval 0.86–0.95, $P < 0.001$) and inferior temporal quadrant for mGCL thickness (AUROC: 0.94, 95%, confidence interval 0.90–0.97, $P < 0.001$) (Table 4).

## Discussion

In this study, we measured mRT and mGCL thickness in glaucomatous and non-glaucomatous patients using the Spectralis SD-OCT PPTM. The mean mRT of the posterior pole in the normal population in this study is compatible with previous studies done with either the PPTM analysis or Early Treatment of Diabetic Retinopathy Study subfield retinal thickness analysis protocol.[8,9 11,15] Our study found greater mean mGCL thickness values in the normal population when compared to a similar study done by Hiroshi *et al.*[2] Their study, however, used a different protocol for measurement of ganglion cell layer thickness without the PPTM's macular segmentation software.

Our results corresponded well with a study by Sandeep *et al.*[6] that found retinal thickness was highest in the nasal field of the Early Treatment of Diabetic Retinopathy Study map. Mean mRT was greater at the nasal quadrant in our study due to the overlap of the temporal vascular arcades. A new OCT segmentation algorithm that excludes retinal vessels from retinal thickness is currently under development to increase the accuracy of OCT parameters. In this study, mean mGCL was thickest at the superior nasal quadrant, followed by the inferior nasal quadrant, similar to a study by Ana *et al.*[5] This finding is most likely attributable to the papillomacular bundle, which is relatively resistant to glaucomatous change and is preserved until the advanced stages of the disease.[16] A literature review also shows that, in the nasal retina, there are 41% more ganglion cells than in the temporal retina.[17]

Our study found that, using the Spectralis SD-OCT PPTM's macular segmentation software, a mean mRT of less than 274.9 µm and mean mGCL thickness of less than 27.9 µm should alert the clinician about the possibility of glaucoma. Both parameters seem to be good predictors to discriminate glaucoma from normal eyes, as both parameters achieve a sensitivity of at least 90% and a specificity of more than 70%. This result is in agreement with results from studies showing that the inner macular layers of the retina are more precise in differentiating between normal and glaucomatous eyes. These measurements also correspond to peripap-

illary retinal nerve fibre layer thickness.[2]

The discrimination ability of mRT and mGCL thickness performed worse with more severe grades of glaucoma. One of the major problems of monitoring structural changes in patients with severe glaucoma by using macular OCT is the floor effect, the point at which no further structural loss is detectable.[18] This floor effect is probably due to the presence of residual tissue such as blood vessels and glial cells.[19]

Comparing between mRT and mGCL thickness, our study demonstrated that mean mGCL thickness has better discriminating capabilities in diagnosing different stages of glaucoma. A study done by Tan *et al.* found that ganglion cell layer thickness measured by SD-OCT has better diagnostic capability compared to the total macular thickness and is statistically equivalent to OCT peripapillary retinal nerve fibre layer measurements.[19] Studies also show that ganglion cell-inner plexiform layer thickness is superior in recognizing glaucoma progression, and is less likely to reach the measurement floor compared to retinal nerve fibre layer thickness in advanced glaucoma.[16, 18]

Macular thickness has been proposed as an early indicator of glaucomatous damage due to the high proportion of retinal ganglion cells present in the macula.[4,8] To increase the diagnostic power of macular imaging, it is useful to isolate the ganglion cell layer from the rest of the retina, as glaucoma causes the death of cell bodies of retinal ganglion cells, which is the main reason for ganglion cell layer thinning.[20] We found that mean mRT and mGCL thickness are especially helpful in diagnosing mild glaucoma and can be used as a biomarker of early glaucomatous damage before visual field defects are evident. Functional visual field loss is only evident when at least 25–40% of retinal ganglion cells have been lost.[6] Significant structural loss of retinal ganglion cells can be revealed 5 years earlier prior to the visual field deficit.[8,9]

The AUROC for mean mRT in the inferior hemisphere was greater than in other quadrants (range 0.859–0.950) in differentiating glaucoma from normal subjects and was statistically significant, $P < 0.001$. This result was similar to those in previous studies showing that inferior macular thickness has high discriminating power with an AUROC range of 0.61–0.83.[15] Our results also suggested that, among all the parameters, mean mGCL thickness at the inferior temporal quadrant has the best diagnostic performance (AUROC: 0.941) in distinguishing glaucoma from normal eyes. A literature review showed that the inferior temporal sector is the most frequent region displaying ganglion cell layer thinning in the macula, which is compatible with the inferior peripapillary area revealing retinal nerve fibre layer defects most commonly.[21]

Our study is not without its limitations. We did not compare the diagnostic accuracy of Spectralis PPTM macular imaging with the more commonly used peripapillary retinal nerve fibre layer measurement. Additionally, we did not compare the diagnostic accuracy of mGCL with the ganglion cell complex, which comprises

the three innermost layers of the retina: the retinal nerve fibre layer, the ganglion cell layer, and the inner plexiform layer. While it has been shown in this study that mean mRT and mGCL thickness measurements perform well in discriminating glaucoma from normal eyes, how it compares to OCT measurements of the retinal nerve fibre layer and ganglion cell complex is beyond the scope of this study. A comparison of the structure-function relationship of macular imaging with the visual field test was also not performed in this study, as this has been done previously in several studies. Lastly, due to the cross-sectional nature of this study, the question of whether macular imaging is useful not only for diagnosis but also for monitoring of glaucoma patients could not be addressed. Future studies could explore this very promising premise on glaucoma patients.

## Conclusion

The Spectralis SD-OCT PPTM offers an alternative imaging method to detect and diagnose early glaucoma. Our study showed that mean mRT and mGCL thickness measured by PPTM has excellent diagnostic accuracy with good sensitivity and specificity to discern between normal and glaucomatous eyes. We would highly recommend its role in diagnostic glaucoma imaging, especially in cases when other methods such as peripapillary retinal nerve fibre layer and/or visual field tests are equivocal.

## Declarations

**Ethics approval and consent to participate**
Ethical approval was obtained prior to the commencement of the study from the Medical Research & Ethics Committee (NMRR-18-458-39979). Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

**Competing interests**
None to declare.

**Funding**
None to declare.

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# Ocular surface conditions in Asian glaucoma patients with existing corneal disorders switching from preserved prostaglandin analogue monotherapy to preservative-free tafluprost

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## Abstract

*Introduction:* Glaucoma medications are often preserved with agents such as benzalkonium chloride, which commonly lead to ocular surface diseases.
*Purpose:* To investigate the effect of switching to a preservative-free prostaglandin analogue, tafluprost 0.0015% on treatment tolerability and ocular surface diseases.
*Study design:* This was a prospective, open-label, non-randomised, observational study performed in a single hospital.
*Materials and methods:* This study involved patients of Asian descent diagnosed with primary open-angle glaucoma and ocular hypertension ($n$ = 28), who received preserved prostaglandin monotherapy for longer than 3 months and had a National Eye Institute ocular surface staining scale score higher than 1. Patients were switched from preserved prostaglandin monotherapy to preservative-free tafluprost 0.0015%. Patients were analysed at baseline (Visit 0), 1 month (Visit 1), and 3 months (Visit 2). The main parameter measured is the change in the fluorescein staining score at Visit 2.
*Results:* There was a significant improvement in the fluorescein staining score,

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with a mean reduction score of 1.96 (standard deviation, SD = 1.53; $p < 0.0001$), and significant reductions in conjunctival hyperaemia (bulbar, $p < 0.0001$; palpebral, $p < 0.05$) from baseline to Visit 2. The Ocular Surface Disease Index questionnaire also showed a mean reduction of 4.14 from baseline to visit 2 (SD = 8.20; $p < 0.05$). The intraocular pressure and tear breakup time were maintained from baseline to Visit 2.

*Conclusion:* Switching patients to preservative-free tafluprost 0.0015% showed significant improvements in ocular surface disease with minimal side effects and similar intraocular pressure reduction rates.

*Keywords:* glaucoma, ocular surface diseases, preservative-free, prostaglandin analogues, tafluprost

# Abstrak

*Pengenalan:* Ubat titis untuk penyakit glaukoma biasanya mengandungi bahan pengawet seperti
benzalkonium klorida, yang kerapkali menyebabkan penyakit permukaan okular.

*Tujuan:* Untuk menyiasat toleransi terhadap rawatan dan kewujudan penyakit permukaan okular berikutan peralihan rawatan kepada prostaglandin analog tanpa bahan pengawet: tafluprost 0.0015%.

*Reka bentuk kajian:* Kajian pemerhatian prospektif tanpa rawak secara label terbuka yang dijalankan di satu pusat kajian.

*Kaedah kajian:* Kajian ini melibatkan pesakit yang menghidap glaukoma sudut terbuka primer (primary open-angle glaucoma) dan hipertensi okular (n = 28), berketurunan Asia yang sedang menerima rawatan ubat titis glaukoma monoterapi: prostaglandin yang mengandungi bahan pengawet selama lebih daripada tiga bulan dan mencatatkan skor bagi skala pewarnaan permukaan mata National Eye Institute (NEI) yang melebihi dari 1. Rawatan kepada pesakit ini kemudian ditukarkan kepada ubat titis prostaglandin tanpa bahan pengawet: tafluprost 0.0015%. Analisa kajian terutama perubahan skor ke atas skala perwarnaan permukaan mata dicatatkan awal kajian (Lawatan 0), sebulan (Lawatan 1), dan tiga bulan (Lawatan 2) selepas rawatan. Dapatan utama kajian ini adalah perbezaan skor skala ini di antara lawatan 0 dan lawatan 2.

*Hasil kajian:* Terdapat perbezaan yang signifikan dalam skor pewarnaan permukaan mata dimana min skor pengurangan sebanyak 1.96 (sisihan piawai, SP =1.53; $p < 0.0001$), dan penurunan yang signifikan hiperemia konjunktiva (bulbus, $p < 0.0001$; palpebra, $p < 0.05$) di antara lawatan 0 dan 2.

Terdapat juga penurunan dari skor soal selidik indeks penyakit permukaan okular (Ocular Surface Disease Index questionnaire) dengan penurunan min sebanyak 4.14 di antara lawatan 0 dan lawatan 2 (SP = 8.20; $p < 0.05$). Manakala

tekanan intraokular dan masa pecahan air mata (tear breakup time) tiada sebarang perubahan di antara lawatan 0 dan 2.
*Kesimpulan:* Peralihan rawatan kepada tafluprost 0.0015% tanpa bahan pengawet memberi pemulihan yang ketara pada permukaan okular tanpa mengurangkan keberkesanan ke atas tekanan intraocular dan kesan sampingan yang minimum ke atas pesakit glauKoma.

*Kata kekunci:* analog prostaglandin, bebas pengawet, glaukoma, penyakit permukaan okular, tafluprost

## Introduction

Glaucoma is a progressive optic neuropathy disease which has been well documented as a significant reason behind irreversible blindness globally.[1,2] Although glaucoma is a multifactorial disease, the only way to slow disease progression and preserve the visual field as proven in literature at the moment is by reducing the intraocular pressure (IOP).[3] For patients with primary open-angle glaucoma (POAG) and ocular hypertension (OH), eye drops are typically used as initial therapy to reduce IOP levels.

At present, prostaglandin analogues (PGA) are the recommended first-line treatment, as there is evidence demonstrating their efficacy in lowering IOP and tolerable safety profile. The most commonly used PGAs are latanoprost, travoprost, bimatoprost, and tafluprost.[4] However, despite their efficacy, these medications are usually preserved with agents such as benzalkonium chloride (BAK), a quaternary ammonium compound with a detergent effect that leads to lysis of bacterial walls and membranes.[5] BAK was first used as a germicide in the 1910s, and then in the 1940s as a preservative in hard contact lens solutions within the ophthalmic industry. It is currently commonly used in most ophthalmic solutions, including artificial tears and glaucoma medications.[6] Latanoprost 0.005% and bimatoprost 0.01% each contain 0.02% BAK, and travoprost 0.004% contains 0.01% polyquaternium-1 (a detergent class of preservative that acts on cell membranes) or a preservative system consisting of zinc, borate, propylene glycol, and sorbitol.[7]

These ophthalmic drops are not a cure for glaucoma; therefore, POAG and OH patients need to consistently remain on prolonged treatment in order to achieve their target IOPs. However, several experimental and clinical studies have demonstrated the association between prolonged exposure to the preservatives (*e.g.*, BAK) in these eye drops and changes in the ocular surface, *e.g.*, tear film lipid layer interference, as well as many ocular surface diseases (OSD), *e.g.*, hyperaemia, dry eyes, or punctate keratitis.[8-10]

Preservative-free (PF) PGAs have been developed to improve long-term toler-

ability. One of them is PF tafluprost 0.0015%, which has been approved by both the US Food and Drug Administration and the European Medicines Agency. There have been a number of studies demonstrating the efficacy of PF tafluprost as an effective IOP-lowering agent.[11] However, only a few studies have evaluated the effect of switching from preserved topical glaucoma medications to PF tafluprost on the ocular surface.[11-16] These studies were comprised of Western patients switching from preserved drops to PF tafluprost and showed a reduction in OSD while maintaining the IOP.

The purpose of this study was to investigate the effect of switching from commonly used preserved PGAs to PF tafluprost on OSD in an Asian population. To evaluate this effect, changes in the fluorescein staining score using the National Eye Institute/Industry (NEI) scale were measured at baseline and subsequently at 4 weeks and 12 weeks after switching to PF tafluprost. Other OSD symptoms were also observed at each visit, along with the IOP-lowering effects.

## Materials and methods

This study is registered in the ClinicalTrials.gov Registry under identifier number NCT04654611. This was a prospective, single-centre, open-label, nonrandomised, observational study carried out at the Tun Hussein Onn National Eye Hospital, Petaling Jaya, Malaysia between January 2019 and December 2019. The sample size was calculated using the G*power software, based on the intended paired t-test analysis in answering the primary study objective. Based on 80% power with a 0.05 two-sided significance level, a minimum of 24 participants were needed, with the assumption of effect size of 0.6.

Twenty-eight POAG or OH patients with OSD caused by preserved PGA therapy were recruited for the study. Recruited patients were required to have a score above 1 on the NEI scale and to have been on PGA monotherapy for more than 3 months. All patients provided their written consent following detailed explanation of the study methodology. This study complied with the principles of the Declaration of Helsinki and the local ethics committee.

First, a thorough anamnesis was established including age, gender, duration of glaucoma diagnosis, type of glaucoma, history of ocular and non-ocular concomitant diseases, and history of ocular surgeries, followed by a detailed ocular examination. Patient compliance was documented at each visit, where patients were asked if they complied every day, most days, some days, or rarely to the study medication.

The primary endpoint was to observe changes in the NEI fluorescein staining score at Visit 2 (week 12). The secondary endpoints included changes in the tear breakup time (TBUT), Ocular Surface Disease Index (OSDI) patient questionnaire, hyperaemia score, IOP, and adverse drug reactions.

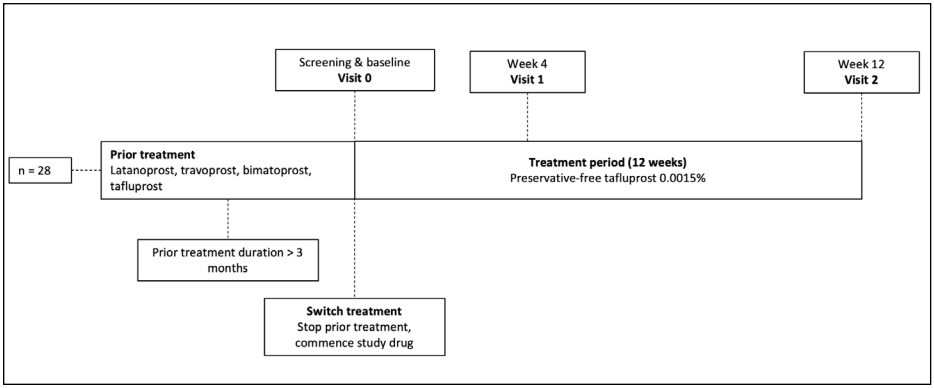


*Fig. 1.* Study design.

To be considered for inclusion, patients were required to be 21 years or older, able to provide informed consent, have OSD due to PGA usage (at least one eye with a score above 1 on the NEI scale), have an IOP of ≤ 21 mmHg in the study eye at the screening examination (under treatment; the eye with a higher NEI score was selected for evaluation), and have received pretreatment monotherapy with any of the following preserved ophthalmic solutions: latanoprost, bimatoprost, tafluprost (these three preserved with BAK), or travoprost (preserved with polyquarternium-1) for a period longer than 3 months. Additional eligibility criteria were best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of +0.6 logMAR (Snellen equivalent of 6/24) in each eye. Those with severe visual field disorder (mean deviation of 15 dB or worse), history of ocular surgeries within 6 months prior to study initiation, severe dry eye, ocular allergy, ocular infection or ocular inflammation, or history of drug allergy were excluded from the study. In addition, patients on systemic or ophthalmic steroids, female patients who were pregnant, nursing, or lactating, contact lens users during the study period, patients with corneal abnormalities or other conditions which could impede accurate applanation tonometry measurements, as well as those with uncontrolled systemic disease such as hypertension or diabetes, were also excluded from the study.

Figure 1 outlines the study design. At baseline (Visit 0), eligible patients who were already on preserved PGAs such as latanoprost 0.005%, bimatoprost 0.01%, tafluprost 0.0015% (these three preserved with BAK), travoprost 0.004% or travoprost 0.003% (these two preserved with polyquarternium-1), for a period longer than 3 months were switched to PF tafluprost 0.0015%. Patients were reviewed again at 4 weeks (Visit 1) and at 12 weeks (Visit 2). During the treatment period, patients were advised to instil PF tafluprost 0.0015% either unilaterally or bilaterally, one drop, once daily, as indicated. The drops were applied at the same hour of the day during the treatment period.

At each follow-up visit (Visit 1 and Visit 2), patients underwent IOP measurement, OSD evaluation (National Eye Institute/Industry [NEI/I] method, TBUT, hyperaemia score), and completed the OSDI questionnaire. Patient compliance and adverse drug reactions were also documented at each visit.

**OSD evaluation**

*NEI/I method*
At every visit, fluorescein dye was instilled in the conjunctival sac of the eye and the fluorescein-stained area of the cornea was measured. The staining degree in each of the five areas of the cornea (central, superior, inferior, temporal and nasal) were scored as follows: none = 0; sparse = 1; dense = 2; coalesced = 3.

*TBUT*
After instilling fluorescein stain, the time (in seconds) until the tear film breaks and the corneal surface is exposed was measured using a slit-lamp microscope. The measurement was conducted three times for one eye and the average of the three scores was recorded as the result.

*IOP measurement*
IOP was measured with Goldmann applanation tonometer at each visit, twice for each measurement. If the two readings differed by ≤ 2 mmHg, the average was recorded as the IOP measurement. If the two readings differed by > 2 mmHg, then a third reading was performed and the median reading was documented.

*Table 1.* The Japanese Guideline for Allergic Conjunctival Diseases clinical evaluation criteria for bulbar and palpebral conjunctiva

| **Bulbar conjunctiva** | | |
|---|---|---|
| i | None | No manifestations |
| ii | Mild | Several vessels dilated |
| iii | Moderate | Many vessels dilated |
| iv | Severe | All vessels dilated |
| **Palpebral conjunctiva** | | |
| i | None | No manifestations |
| ii | Mild | Several vessels dilated |
| iii | Moderate | Many vessels dilated |
| iv | Severe | Individual blood vessels indistinguishable |

Adapted from Takamura *et al.*[17]

*Hyperaemia score*
Bulbar and palpebral conjunctiva was examined and scored using reference photographs and a four-step scale. This four-step scale is cited from the clinical evaluation criteria of the Japanese Guideline for Allergic Conjunctival Diseases (Table 1).[17]

*OSDI questionnaire*
The OSDI questionnaire was used to evaluate OSD symptoms. It is a 12-item questionnaire frequently used to evaluate OSD severity.[18] OSD symptoms, limitations in function related to vision, and environmental factors were assessed and scored from 0 (none) to 4 (all the time). The OSDI score was then obtained as follows:

$$\text{Total score} = \frac{\text{Sum of the score for all the questions answered} \times 100}{\text{Number of questions answered} \times 4}$$

The total score ranges from 0 to 100. A score of 0–12 points indicated normal ocular surface, 13–22 points mild disease, 23–32 points moderate disease, and ≥ 33 points severe disease.[19] The primary and secondary endpoints in this study were analysed both descriptively and inferentially using the parametric paired t-test. Wilcoxon signed rank test was applied when the assumptions for paired t-test were not fulfilled. $P < 0.05$ was considered statistically significant.

## Results

### Demographics and clinical characteristics

A total of 28 patients were enrolled, with 24 patients (85.7%) completing this study. The sociodemographic characteristics analysis revealed that the majority of the participants were male (*n* = 19; 67.9%) and of Chinese descent (*n* = 24; 85.7%). Age ranged from 45 to 84 years old, with an average age of 65.5 (standard deviation, SD = 9.55) years. Analysing the clinical characteristics of the participants, the study involved more of right-eye patients than left-eye patients (*n* = 17; 60.7% *versus n* = 11; 39.3%) (Table 2). Most participants were diagnosed as POAG (*n* = 26; 92.9%) followed by OH (*n* = 2; 7.1%), as shown in Figure 2.

### Primary endpoint

*Changes in NEI corneal fluorescein staining score at Visit 2*
There was an overall mean reduction in the corneal fluorescein staining (CFS) scoring of 1.96 from baseline to Visit 2 (SD = 1.53) when compared to the entire cornea (Fig. 3). The maximum CFS scoring reduction from baseline to Visit 2 was 6, while the minimum CFS scoring reduction from baseline to Visit 2 was 0 (Fig. 3). No increased CFS scoring was noted at Visit 2 compared to baseline. The differences

*Table 2.* Baseline demographic and clinical characteristics ($n = 28$)

| Variables | Frequency (%) |
|---|---|
| Gender | |
| Male | 19 (67.9) |
| Female | 9 (32.1) |
| Ethnicity | |
| Chinese | 24 (85.7) |
| Indian | 3 (10.7) |
| Malay | 1 (3.6) |
| Age (years) | |
| Mean | 65.5 (SD = 9.55) |
| Minimum | 45 |
| Maximum | 84 |
| RE/LE | |
| RE | 17 (60.7) |
| LE | 11 (39.3) |

LE: left eye; RE: right eye; SD: standard deviation

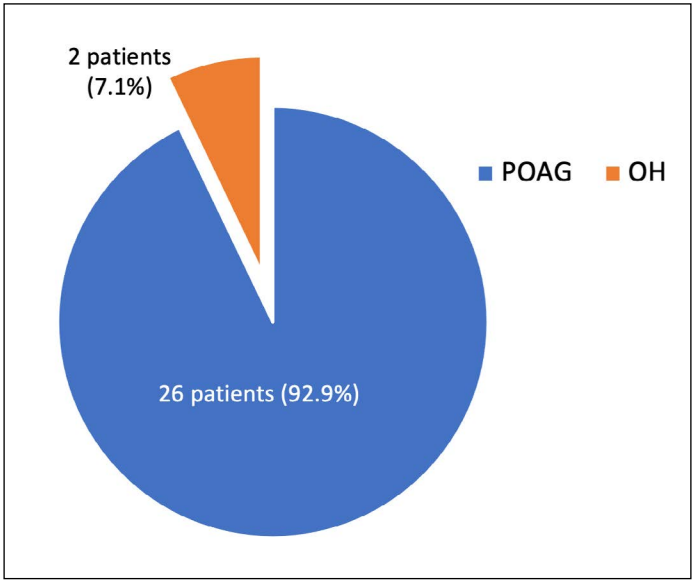


*Fig. 2.* Distribution of patient diagnosis. OH: ocular hypertension; POAG: primary open-angle glaucoma.

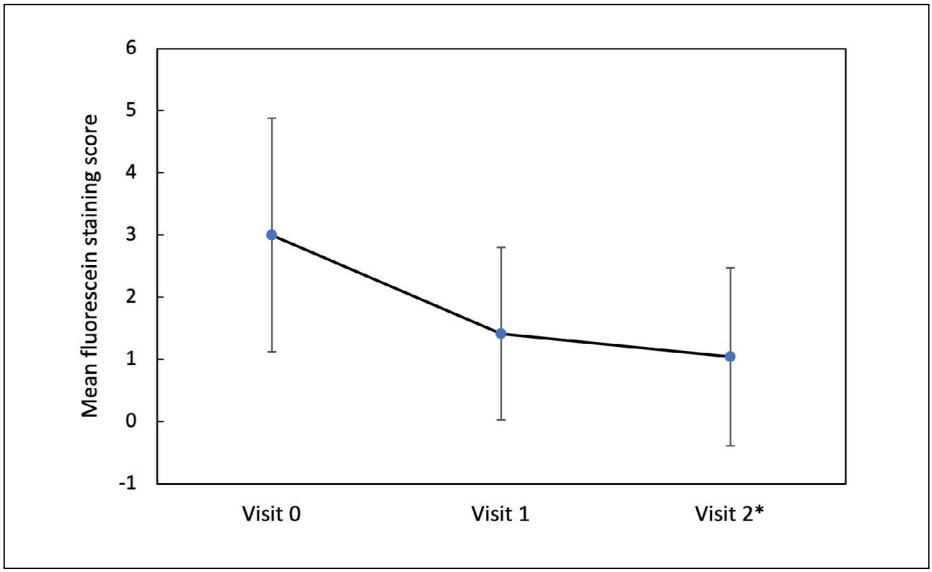


*Fig. 3.* Mean fluorescein staining scores (according to the National Eye Institute ocular surface staining scale) at baseline (Visit 0) and after switching patients from preserved prostaglandin analogue monotherapy to preservative-free tafluprost (Visits 1 and 2). Standard deviations are indicated by error bars. * indicates $p < 0.0001$ *vs* Visit 0.

in CFS scoring between these two points were found to be statistically significant ($p < 0.0001$) based on the Wilcoxon signed rank test.

**Secondary endpoints**

*Changes in TBUT at Visit 2*

There was an overall mean reduction of TBUT scoring by 0.22 from baseline to Visit 2 (SD = 2.41). The maximum TBUT scoring reduction from baseline to Visit 2 was 7. The maximum increase in TBUT scoring was 4 at Visit 2 compared to baseline. The differences in TBUT scoring between these two points were not found to be statistically significant ($p > 0.05$; 95% confidence interval, CI: -0.73–1.18) based on paired t-test.

*Changes in OSDI patient questionnaire at Visit 2*

The OSDI questionnaire was used to evaluate OSD symptoms. There was an overall mean reduction of OSDI scoring by 4.14 from baseline to Visit 2 (SD = 8.20). The maximum OSDI scoring reduction from baseline to Visit 2 was 31. The maximum increase in OSDI scoring was 2 at Visit 2 compared to baseline. The differences in OSDI scoring between these two points were found to be statistically significant ($p < 0.05$) based on the Wilcoxon signed rank test.

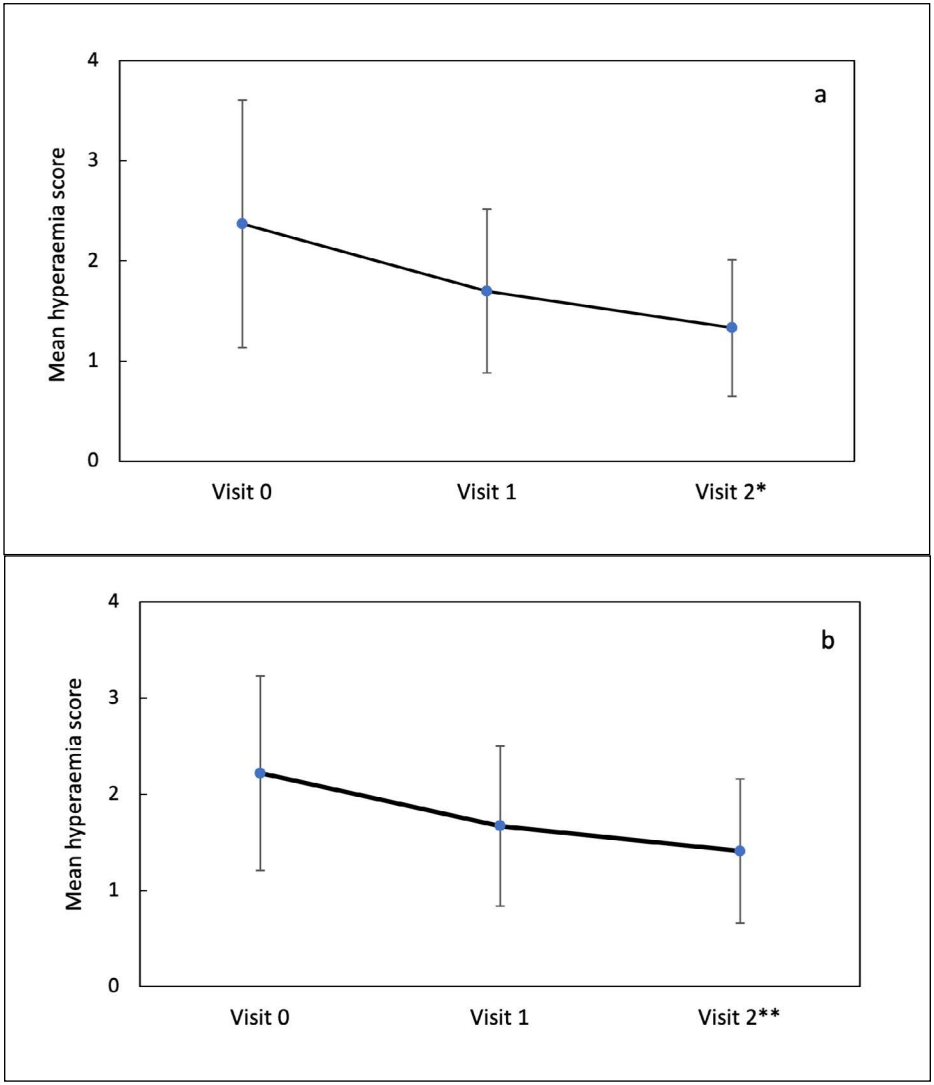


*Fig. 4.* (*a*) Mean bulbar and (*b*) mean palpebral hyperaemia scores at baseline (Visit 0) and after switching patients from preserved prostaglandin analogue monotherapy to preservative-free tafluprost (Visits 1 and 2). Standard deviations are indicated by error bars.
* indicates $p < 0.0001$ *vs* Visit 0; ** indicates $p < 0.05$ *vs* Visit 0.

*Changes in hyperaemia at Visit 2*

Bulbar conjunctiva

There was an overall mean reduction of hyperaemia scoring by 1.04 from baseline to visit 2 (SD = 1.26) (Fig. 4a). The maximum hyperaemia scoring reduction from baseline to Visit 2 was 6, with minimum score reduction of 0 from baseline to visit 2. No increase in hyperaemia was noted at the end of Visit 2. The differences in hyperaemia scoring between these two points were found to be statistically significant ($p < 0.0001$) based on the Wilcoxon signed rank test.

Palpebral conjunctiva

There was an overall mean reduction of hyperaemia scoring by 0.81 from baseline to visit 2 (SD = 0.96) (Fig. 4b). The maximum hyperaemia scoring reduction from baseline to Visit 2 was 3. The maximum increase in hyperaemia scoring was 1 at Visit 2 compared to baseline. The differences in hyperaemia scoring between these two points were found to be statistically significant ($p < 0.05$) based on the Wilcoxon signed rank test.

*Changes in IOP at Visit 2*

There was an overall mean increase of IOP by 0.30 mmHg from baseline to Visit 2 (SD = 2.22). The maximum IOP reduction from baseline to Visit 2 was 5 mmHg. The maximum increase in IOP was 4 mmHg at Visit 2 compared to baseline. The differences in IOP between these two points were found to be not statistically significant ($p > 0.05$; 95% CI: -1.17-0.58) based on paired t-test. Switching drops did not cause harmful fluctuations or alter the patients' IOP overall.

**Adverse drug reactions**

Three out of 28 patients (10.7%) recorded drug reactions in this study. The reactions were itchiness ($n = 3$), redness ($n = 1$), and burning sensation ($n = 1$). No systemic adverse reaction was recorded. All adverse reactions were mild and resolved after discontinuing the medication.

## Discussion

IOP is typically the only variable that is treated or controlled in glaucoma patients. Due to the chronic and progressive nature of the condition, patients are usually on long-term topical drops that typically contain high levels of preservatives.

The purpose of this study was to investigate the effect of switching patients from commonly used preserved PGAs to PF tafluprost on OSD in an Asian population. Previous switch studies conducted on Asian eyes have been retrospective studies looking at varying glaucoma diagnoses, or prospective studies involving patients

switched from different classes of medications or from a specific eyedrop only.[20,21] This study has the advantage of being a prospective study specifically evaluating POAG and OH patients switching from preserved PGA class to PF tafluprost in a multiethnic Asian population. Even though most glaucoma patients can tolerate preserved PGAs, a large number of patients do suffer from OSD caused by preservatives, specifically BAK. BAK contains a combination of alkylbenzyldimethylammonium chlorides, which are toxic to microorganisms as well as eukaryotic cells. This may contribute to ocular surface side effects such as conjunctival hyperaemia, tear film instability, dry eye, and burning sensation.[22,23]

A significant reduction in the number of patients exhibiting subjective symptoms during PF tafluprost treatment was noted, evidenced by the OSDI questionnaire showing a mean reduction of 4.14 from baseline to Visit 2 (SD = 8.20; $p < 0.05$). PF tafluprost maintained IOP with no significant change from baseline throughout the treatment period of 3 months. There were no significant changes noted for TBUT as well; this could have been attributed to the short study duration, as longer observations would be needed to see improvement in TBUT. There was a significant improvement in the NEI CFS score with a mean score reduction of 1.96 (SD = 1.53; $p < 0.0001$) and significant reductions in conjunctival hyperaemia (bulbar, $p < 0.0001$; palpebral, $p < 0.05$). Itchiness was the most common adverse effect documented. It was also found that 89.3% of the patients were compliant to the treatment and rarely missed doses. We hypothesise that the high compliance rate could be directly related to the tolerability and reduced ocular side effects of the PF eye drop.

It should also be pointed out that this study had some limitations, as the sample size was small and the treatment period was only 12 weeks. A longer treatment period may be necessary to evaluate potential long-term benefits of the PF tafluprost preparation, such as visual field stability and enhanced ocular blood flow.[24-26] The study was not blinded and this could have led to investigator bias in the results. However, the patient outcomes were reported in accordance to the protocol, which was adhered to by the investigator and his team.

In conclusion, PF tafluprost was better tolerated than commercially available preserved PGA formulations in patients recruited in this study. The high compliance rate of patients also provides an indication of improved adherence in those switching from preserved drops. PF tafluprost 0.0015% showed significant improvements in OSD with minimal side effects and similar IOP reduction rates.

## Declarations

### Ethics approval and consent to participate

This study is registered in the ClinicalTrials.gov Registry under identifier number NCT04654611. All patients provided their written consent following detailed

explanation of the study methodology. This study complied with the principles of the Declaration of Helsinki and the local ethics committee.

**Competing interests**
The authors declare no competing interests.

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# Subthreshold 577 nm laser photocoagulation vesus conventional 532 nm laser photocoagulation for diabetic macular oedema

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## Abstract

*Purpose:* To evaluate the visual and anatomic outcomes of the subthreshold micropulse 577 nm yellow diode laser (MYL) and to compare its efficacy with the conventional green 532 nm diode laser (CGL) in Asian eyes with diabetic macular oedema (DME).
*Study design:* Prospective randomized controlled clinical trial
*Methods:* Sixty-seven eyes of 43 patients with clinically significant macular oedema (CSME) were randomized to receive either MYL ($n = 37$) or CGL ($n = 30$) at baseline and were followed up for 12 months. Titration in the MYL group was performed with 15% duty cycle, 300 ms duration, and double the threshold power, while the modified Early Treatment of Diabetic Retinopathy Study (mETDRS) protocol was used for the CGL arm with the power titrated to a barely visible burn. Parameters noted included best-corrected visual acuity (BCVA) (logMAR), central subfoveal thickness (CST), macular volume (MV), and average macular thickness (AMT) using optical coherence tomography, and presence of visible laser scars on colour fundus photographs and fundus autofluorescence, at baseline and at 12 months.
*Results:* At 12 months follow-up, BCVA improved by 4.7 and 8.8 letters, respectively, for the MYL and CGL treatment arms ($p < 0.05$). There was a significant reduction in all retinal thickness parameters (CST, MV, and AMT) when compared to baseline

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in both laser treatment arms at 12 months. There was no significant difference in either BCVA or retinal thickness parameters between the two treatment arms at 1, 3, 6, 9, or 12-month follow-up. Laser scars were observed in 26.7% of patients in the MYL group compared to 75% of patients in the CGL group ($p = 0.029$).
*Conclusions:* MYL is an effective, safe, and patient-friendly treatment option for clinically significant macular oedema, with improvement in BCVA, reduction in macular thickness, and less scarring after treatment at 12 months.

*Keywords:* clinically significant macular oedema, diabetic macular oedema, subthreshold laser photocoagulation, subthreshold yellow laser

# Abstrak

*Tujuan:* Untuk membandingkan keberkesanan di antara mikropulse subthreshold 577 nm laser diod kuning (MYL) dan laser diod 532 nm (CGL) konvensional pada pesakit diabetis berasal dari Asia yang mengalami edema macular ("diabetic macular edema" [DME]) dari segi penglihatan dan anatomi makular.
*Reka bentuk kajian:* Kajian klinikal terkawal prospektif secara rawak
*Kaedah kajian:* Kajian ini melibatkan 67 mata dari 43 pesakit diabetis dengan edema makula yang signifikan secara klinikal ("clinical significant macular edema" [CSME]) secara rawak untuk menerima rawatan laser samada MYL ($n = 37$) atau CGL ($n = 30$) pada permulaan rawatan dan disusulkan selama 12 bulan. Dalam kumpualan MYL, titrasi dilakukan dengan 15% kitaran selama 300 ms dan menggandakan daya ambang. Sementara rawatan modifikasi protokol "Early Treatment of Diabetic Retinopathy Study" (mETDRS) digunakan bagi kumpulan CGL dengan dititrasikan dengan kesan parut pembakaran laser yang hampir tidak kelihatan pada makular. Ketajaman penglihatan yang terbaik setelah diperbetulkan ("best corrected visual acuity" [BCVA]) menggunakan unit logaritma sudut resolusi minimum (logMAR) dan parameter anatomi termasuk ketebalan subfoveal tengah (CST), isipadu makular (MV) dan purata ketebalan makula (AMT) menggunakan tomografi koheren optikal (OCT) , beserta kesan parut pembakaran laser pada retina yang dikesan melalui foto dan autofluoresensi pada foto fundus. Semua parameter ini didokumentasikan pada peringkat permulaan rawatan dan setelah 12 bulan selepas rawatn.
*Keputusan:* Pada 12 bulan susulan selepas rawatan, BCVA meningkat sebanyak 4.7 huruf bagi kumpulan MYL dan 8.8 huruf untuk kumpulan CGL ($p < 0,05$). Terdapat penurunan yang signifikan dalam semua parameter ketebalan retina (CST, MV, dan AMT) berbanding bacaan pada permulaan rawatan bagi kedua-dua kumpulan. Tetapi tiada perbezaan yang signifikan dari segi ketajaman penglihatan BCVA mahupun parameter melibatkan ketebalan retina pada 1, 3, 6, 9 atau 12 bulan susulan di antara kedua-dua kumpulan. Kesan laser dapat dilihat pada 26.7% pesakit

dalam kumpulan MYL berbanding 75% pesakit dalam kumpulan CGL ($p = 0.029$). *Kesimpulan:* MYL adalah efektif untuk rawatan CSME dari segi peningkatan BCVA dan mengurangkan ketebalan macula secara anatomi, mengurangkan kesan parut dan mesra pesakit selepas rawatan pada 12 bulan.

*Kata kekunci:* clinically significant macular oedema, diabetic macular oedema, subthreshold laser photocoagulation, subthreshold yellow laser

## Introduction

Diabetic macular oedema (DME) is the most common cause of moderate visual loss in the working-age population in patients with diabetes mellitus (DM), with a 10-year cumulative incidence of 20.1% and 25.4% for patients with type 1 and 2 DM, respectively.[1,2] The landmark Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that argon laser photocoagulation decreases the risk of moderate visual loss in clinically significant macular oedema (CSME) by 50% and was the mainstay of treatment for many years.[3,4] However, the conventional laser uses continuous-wave energy that produces a visible burn on the retina and has several complications such as scotomas, visual field defects, chorioretinal atrophy, macular creep, choroidal neovascularization, and subretinal fibrosis.[5-7]

To address these risks and to reduce potential collateral damage, the subthreshold diode laser was introduced. In 1997, Friberg and Karatza first reported the clinical application of subthreshold micropulse 810 nm diode laser treatment in DME[8] and several studies have demonstrated its efficacy in different macular diseases.[9-14] Subthreshold micropulse laser treatment uses a shorter exposure time and a subvisible clinical endpoint (in which no coagulation spot is observed), delivering laser energy by dividing the beam into a series of short laser pulses (100–300 µs). Every single pulse has an on and off duration (duty cycle), enabling tissues to cool down to baseline temperature before the next pulse.[15] By using a low laser power, it avoids protein coagulation and targets almost selectively the melanocytes within the retinal pigment epithelium (RPE), with minimum damage to the neural retina and choroidal layers.[16]

The beneficial effect of a subthreshold laser works by reducing Müller cell activation, as well as decreasing production of cytokines and vasoactive substances, thus leading to less capillary permeability, suppression of vascular endothelial growth factor (VEGF), and upregulation of pigment epithelium-derived factor (PEDF), and improving retinal function, stabilizing visual acuity, and decreasing macular oedema.[17-20]

The subthreshold micropulse diode laser is available in different wavelengths: 532 nm, 577 nm, or 810 nm. Theoretically, yellow (577 nm) wavelength diode lasers offer some advantages for macular tissues as they are not absorbed by the

xanthophyll pigment in the macula, thereby allowing retreatment sessions and application directly to the centre of the fovea.[13,20] It is better absorbed by RPE melanin and haemoglobin compared to the 810 nm infrared laser wavelength and causes less scatter compared to 532 nm, thereby allowing use of lower powers and shorter pulse durations.[20]

We conducted a prospective, randomized controlled clinical trial to evaluate the visual and anatomic outcomes of the subthreshold 577 nm yellow diode laser (MYL) and compare its efficacy with the conventional green 532 nm diode laser (CGL) in Asian eyes with DME.

## Methods

### Study design

This study was a prospective, randomized, controlled clinical trial performed at the Eye Clinic of University of Malaya Medical Centre (UMMC) from August 2009 to December 2011. The study was approved by the UMMC Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. This study was listed on www.clinicaltrials.gov, under identifier NCT01045239.

### Patient selection

Patients with type 2 DM with DME were enrolled from the Eye Clinic of UMMC in a consecutive if eligible basis. Eligibility criteria included diagnosis of CSME using the ETDRS criteria[3] on biomicroscopy and best-corrected visual acuity (BCVA) between 15 and 68 letters on the modified ETDRS chart (logMAR 1.0).

The exclusion criteria included macular oedema caused by a disease other than diabetes; pre-existing ocular conditions that can interfere with visual acuity improvement (foveal atrophy, pigment abnormalities, dense subfoveal hard exudates, significant macular ischemia, vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, etc.); dense media opacity; history of treatment for DME at any time in the previous 4 months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs); history of panretinal photocoagulation (PRP) within 4 months prior to enrolment or anticipated to be performed within the next 6 months, and history of major ocular surgery (including vitrectomy, cataract extraction, scleral buckle, or any intraocular surgery, etc.) within the previous 4 months or anticipated within the next 6 months.

Patients were randomly assigned to receive treatment with MYL or CGL using sequentially numbered, opaque sealed envelopes (SNOSE). At the initial visit, a detailed history was recorded for all patients including duration of DM, past glycaemic control ($HbA_1c$), medications, and general medical and ocular history. All patients were examined at baseline and at 1, 3, 6, 9, and 12 months after treatment.

At each visit, patients underwent BCVA measurement, slit lamp biomicroscopy, fundus photography, and macular thickness measured by spectral-domain optical coherence tomography (SD-OCT) (Cirrus HD OCT version 5.0, Carl Zeiss Meditec, Dublin, USA). For SD-OCT measurement, three parameters were recorded: central subfoveal thickness (CST), macular volume (MV), and average macular thickness (AMT). Fundus fluorescein angiography (FFA) was done if deemed necessary by the assessing ophthalmologist to assess macular ischaemia or leakage. Fundus colour photographs and fundus autofluorescence (FAF) imaging were performed on all patients. The images taken at baseline and at 12 months follow-up were graded by an independent centre, the Singapore Advanced Imaging Laboratory for Ocular Research (SAILOR), Singapore Eye Research Institute, in order to identify new laser scars. During follow-up, the patients were assessed by an independent data collector for visual acuity, SD-OCT measurements, and fundus photos. Clinical assessment, including noting of macular scars on slit lamp biomicroscopy was done by another investigator who was blinded to the treatment patients had received. The treating ophthalmologists were not involved in follow-up assessments of the patients.

**Treatment technique**

CGL was performed with a 532 nm diode green laser light using the Zeiss Visulas diode laser (Carl Zeiss Meditec, Jena, Germany). We followed the modified-ETDRS technique of 100 µm spot sizes with an exposure time of 100 ms. The power was adjusted by slowly increasing the laser power until a light grey-white (just visible) burn was obtained.[21] Treatment was performed up to 500 µm from the centre of the foveal avascular zone.

MYL was performed using laser light at 577 nm using a Quantel Supra 577 diode laser (Quantel Medical, Cedex, France). The subthreshold laser power was derived from a test burn. The test burn was performed in the continuous wave mode using a 100 µm spot diameter and a 300 ms duration in the nasal side outside the vascular arcade with the power titrated until a burn became barely visible.[11] The diode laser was switched from continuous wave emission mode to subthreshold emission mode at 15% duty cycles, 300 ms duration, and the power to achieve the visible laser burn doubled. Treatment was applied in a confluent fashion to the entire area of macular oedema without any visible burns on the retina.

If there was little or no improvement of the condition, laser treatment was repeated at 16 weeks intervals, with a maximum of three treatment sessions. Patients with recalcitrant macular oedema were offered other treatment options after the maximum three laser sessions.

**Statistical analysis**

The paired t-test was used to test for significant mean deviation of the four parameters: BCVA, CST, AMT, and MV at five time periods (1, 3, 6, 9 and 12 months

after treatment) against the baseline within the CGL and MYL treatment arms. To test whether the mean deviation in the CGL treatment arm differed significantly from that of the MYL treatment arm, the two-sample t-test was used. Bonferroni adjustment to the significance level of 5% was done in the five comparisons, resulting in actual significance level of 1.7% per test.

Patients within each laser treatment group were further stratified into two groups based on:

i. CST levels at baseline (400 µm or higher; below 400 µm)
ii. oedema type (focal or diffuse).

Focal oedema was defined as having fewer than four parafoveal OCT quadrants greater than 300 µm and diffuse oedema was defined as having all four parafoveal quadrants greater than 300 µm in thickness.[19]

Two-factor ANOVA was used to check for interaction between laser treatment and the stratifying variable. This was followed by two-sample t-tests (for six time points) between the levels of the stratifying variable within a particular laser treatment arm, and then between laser treatments within a particular level of the stratifying variable. As six separate tests were done, Bonferroni adjustment to the significance level of 5% resulted in actual significance level of 0.8% per test.

The presence of visible macular scars at 12 months was also compared to baseline. Chi-square test (Pearson chi-square) was used to assessed statistical difference. A $p$-value < 0.05 was considered to be significant. The statistical analyses were carried out using R version 2.13.1 (R Development Core Team, 2011).

*Table 1.* Clinical characteristics of patients at baseline in the green and yellow laser treatment arms

| **Characteristics** | **MYL ($n$ = 37) Mean (SD)** | **CGL ($n$ = 30) Mean (SD)** | ***p*** |
|---|---|---|---|
| Age (years) | 59.4 (7.5) | 61.1 (7.6) | 0.677 |
| Diabetic duration (years) | 15.0 (7.0) | 12.7 (5.8) | 0.142 |
| HbA1c (%) | 8.6 (1.7) | 8.9 (1.7) | 0.654 |
| Diastolic blood pressure (mmHg) | 78.6 (11.2) | 78.3 (11.3) | 0.905 |
| Systolic blood pressure (mmHg) | 143.2 (18.0) | 144.1 (28.6) | 0.866 |
| BCVA (letters) | 36.3 (12.1) | 34.5 (14.6) | 0.548 |

Values shown are mean values. The standard deviation (SD) is stated in parentheses.
BCVA: best-corrected visual acuity; MYL: micropulse yellow laser; CGL: conventional green laser

*Table 2.* Classification of oedema and number of laser treatment for eyes in the CGL and MYL treatment groups

| | Type of Oedema | | | | | | Number of laser treatments | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Diffuse** ***n*** **(%)** | **Focal** ***n*** **(%)** | **Total** ***n*** **(%)** | **CST < 400 µm** ***n*** **(%)** | **CST ≥ 400 µm** ***n*** **(%)** | **Total** | **1** | **2** | **3** | **Total (Average)** |
| **CGL** | 17 (57%) | 13 (43%) | 30 | 23 (77%) | 7 (23%) | 30 | 9 | 18 | 3 | 30 (1.8) |
| **MYL** | 28 (76%) | 9 (24%) | 37 | 24 (65%) | 13 (35%) | 37 | 12 | 17 | 8 | 37 (1.9) |

MYL: micropulse yellow laser; CGL: conventional green laser; CST: central subfoveal thickness

## Results

Sixty-seven eyes of 43 patients (20 men and 23 women) completed follow-up at 12 months. Thirty-seven eyes received MYL and 30 eyes received CGL. The mean age was 60.25 ± 7.5 years. The mean duration of DM was 14.3 ± 6.52 years and the mean HbA1c at baseline visit was 8.7 ± 1.6%. There were no significant differences in parameters between the two laser arms at the baseline visit (Table 1).

In the subgroup analysis, 23% of patients in the CGL arm and 35% of patients in the MYL arm had a baseline CST of > 400 µm (Table 2). There were 76% of patients with diffuse oedema in the MYL arm compared with 57% in the CGL arm.

### Visual acuity

At baseline, mean BCVA was 36.3 (standard deviation, SD 12.1) in the MYL arm and 34.5 (SD 14.6) in the CGL arm. Eyes in both treatment arms showed statistically significant improvement in mean BCVA 12 months after treatment, with a gain of 4.7 letters in the MYL group [95% confidence interval (CI): 0.9, 8.4; $p < 0.01$] and 8.8 (95% CI: 3.9, 13.7; $p < 0.01$] letters in the CGL group (Fig. 1). However, there was no statistical difference in mean BCVA from baseline to 12 months between both treatment arms, $p = 0.44$.

### Macular thickness

Mean CST at baseline was 353.64 µm in the MYL arm and 351.38 µm in the CGL arm. At 12 months follow-up, the mean reduction in CST was 65.7 µm in the MYL arm (95% CI: -104.5, -27; $p < 0.01$) and 58.5 µm in the CGL arm (95% CI: -107.8, -9.2; $p < 0.01$) (Fig. 2).

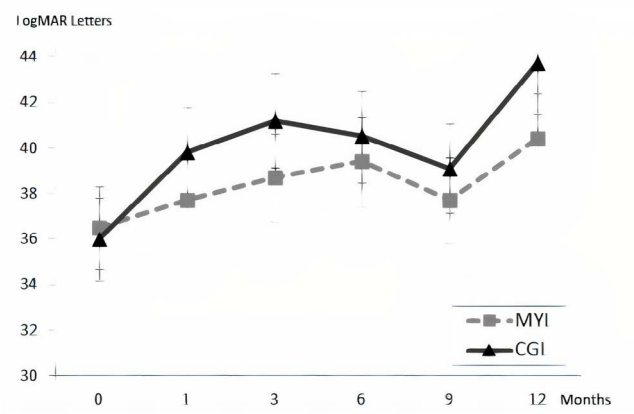


*Fig. 1.* Visual acuity of patients in the micropulse yellow laser (MYL) and conventional green laser (CGL) treatment groups at baseline and 1, 3, 6, 9, and 12 months after treatment.

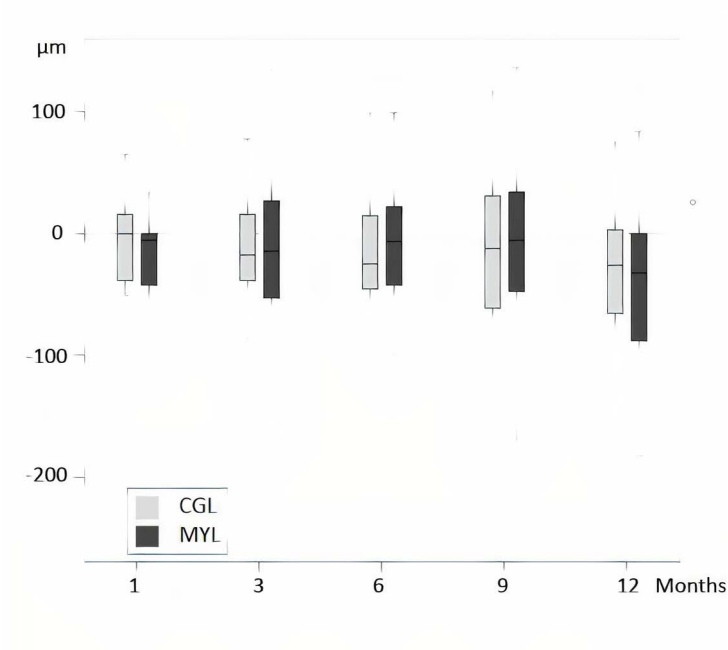


*Fig. 2.* Changes in central subfield thickness of patients in the micropulse yellow laser (MYL) and conventional green laser (CGL) treatment groups at baseline and 1, 3, 6, 9, and 12 months after treatment.

There was no statistical difference in the reduction in CST from baseline to 12 months between both treatment arms ($p = 0.67$).

Mean MV at baseline was 11.37 $mm^3$ in the MYL arm and 10.60 $mm^3$ in the CGL arm. Mean reduction in MV at 12 months was 0.88 $mm^3$ in the MYL arm (95% CI: -1.3, -0.3; $p < 0.01$) and 0.69 $mm^3$ in the CGL arm (95% CI: -1.0, -0.2; $p < 0.01$), with no significant difference between both treatment arms ($p = 0.43$).

Mean AMT at baseline was 315.81 µm in the MYL arm and 300.63 µm in the CGL arm. At 12 months follow-up, the mean reduction in AMT was 24.4 µm in the MYL group (95% CI: -39.5, -9.4; $p < 0.01$) and 16.1 µm in the CGL group (95% CI: -28.2, -4.1; $p < 0.01$), with no significant difference between both arms ($p = 0.88$).

**Subgroup analysis**

For the subgroup analysis of CST ≥ 400 µm and < 400 µm, there was no statistically significant difference in BCVA in both the CGL and MYL arms at 12 months follow-up. However, the CST ≥ 400 µm subgroup showed significant reduction in thickness

*Table 3.* Difference in mean improvement in BCVA and CST at 12 months compared to baseline between the subgroups with baseline CST < 400 µm and ≥ 400 µm

| | **Yellow** | | | **Green** | | |
|---|---|---|---|---|---|---|
| | **Baseline CST < 400 µm Mean (SD)** | **Baseline CST ≥ 400 µm Mean (SD)** | **p** | **Baseline CST < 400 µm Mean (SD)** | **Baseline CST ≥ 400 µm Mean (SD)** | ***p*** |
| **BCVA** | 3.1 (10.6) | 4.2 (8.5) | 0.99 | 7.4 (7.5) | 9.3 (12.5) | 0.83 |
| **CST** | 8.9 (64.5) | 117.6 (90.0) | 0.01 | 21.4 (42.5) | 130.7 (117.1) | **0.03** |

BCVA: best-corrected visual acuity; CST: central subfoveal thickness

*Table 4.* Difference in mean improvement in BCVA and CST at 12 months compared to baseline between the focal and diffuse subgroups

| | **Yellow** | | | **Green** | | |
|---|---|---|---|---|---|---|
| | **Focal Mean (SD)** | **Diffuse Mean (SD)** | **p** | **Focal Mean (SD)** | **Diffuse Mean (SD)** | ***p*** |
| **BCVA** | 3.3 (5.8) | 5.4 (8.3) | 0.19 | 8.0 (9.4) | 9.25 (9.0) | 0.47 |
| **CST** | 25.1 (42.7) | 62.1 (88.0) | 0.58 | 35.2 (46.7) | 60.3 (101.1) | 0.50 |

BCVA: best-corrected visual acuity; CST: central subfoveal thickness

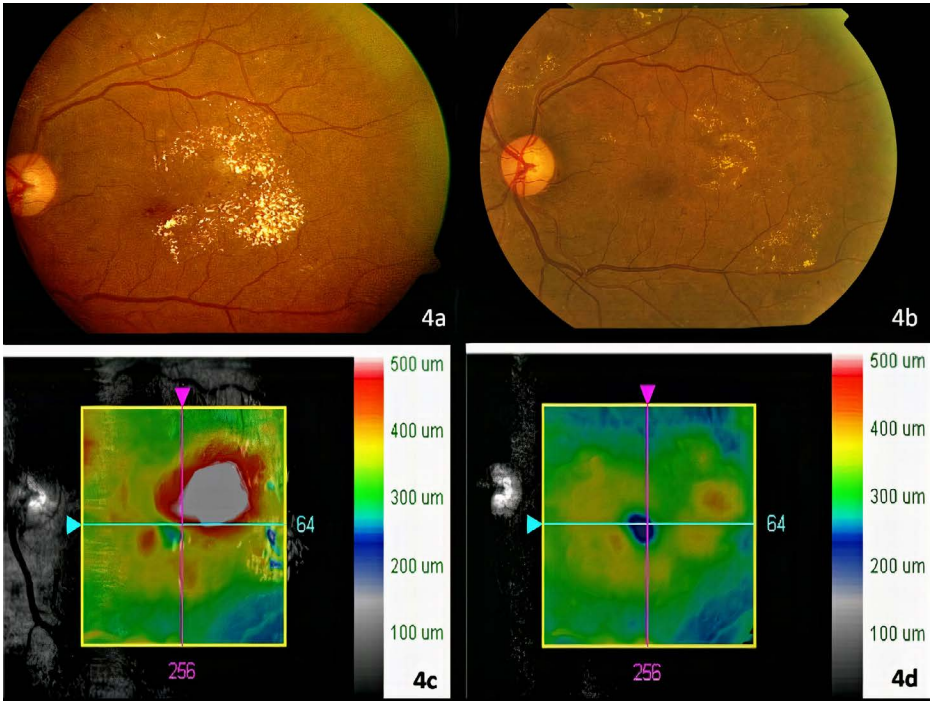


*Fig. 3.* Composite image showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with micropulse yellow laser. The oedema resolved and visual acuity improved from 37 letters to 57 letters. No laser scars were seen at the macula.

compared to the CST < 400 µm subgroup in both treatment arms (Table 3). There was no significant difference in BCVA or improvement in CST between the focal and diffuse DME groups in both the CGL and MYL arms at 12 months follow-up (Table 4).

**Laser scars**

Seventy-five percent of eyes in the CGL arm showed visible scarring on slit lamp biomicroscopy and/or fundus photographs at 12 months follow-up compared to only 26.7% in the MYL arm, $p < 0.001$. FAF of the laser scars, either decreased or increased FAF, were detected in 88.9% and 41.7% of eyes in the CGL and MYL laser groups, respectively, $p = 0.003$. Figures 3 and 4 are composite images showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with MYL and CGL, respectively.

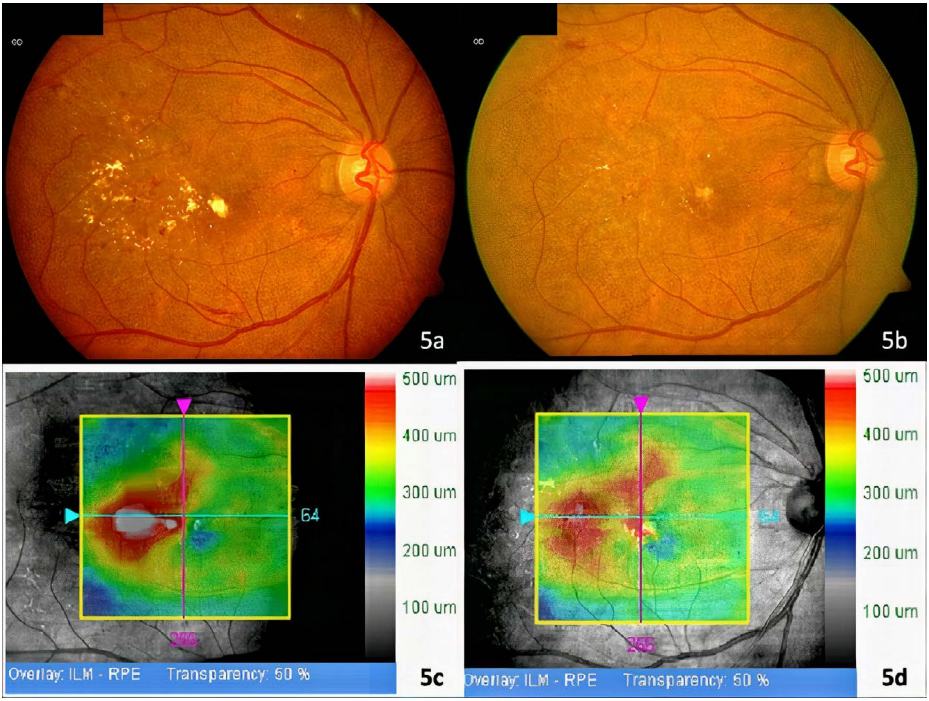


*Fig. 4.* Composite image showing colour fundus photographs of the macula and SD-OCT images at baseline and 12 months after treatment with conventional green laser. Note the presence of laser scars temporal to the macula.

## Discussion

The World Health Organization has estimated Malaysia will have a total of 2.48 million people with DM by 2030.[22] The Singapore Malay Eye Study on 3,280 Malay adults 40 to 80 years with DM revealed a 35.0% prevalence of any form of diabetic retinopathy; 4.9% with proliferative DR and 35.0% with macular oedema.[23] Intravitreal anti-VEGF and steroids are the current treatment of choice in management of DME.[24-26] Nevertheless, intravitreal anti-VEGFs require repeated injections and frequent visits to maintain the visual and anatomic gains, causing a huge economic burden. Also, DME is sometimes resistant to these therapies and may require other treatment modalities.[27]

Subthreshold laser is a novel, tissue-sparing approach to treat DME that preserves macular function and causes less iatrogenic damage to the tissues surrounding the area of the burn in the RPE. While most of the initial studies on subthreshold laser used the 810 nm infrared laser, some studies have explored the use of 532 nm green

and 577 nm yellow lasers for the treatment of DME. In this randomized controlled trial, we showed that the subthreshold 577 nm yellow laser was as effective as conventional modified-ETDRS green laser photocoagulation in the treatment of DME, with a much lower incidence of scarring at 12 months.

We found significant improvement in BCVA in both treatment arms at 12 months, (8.8 letters in the CGL arm *versus* 4.7 letters in the MYL arm improvement; $p = 0.44$). All 3 SD-OCT parameters (CST, MV, and AMT) measured showed a statistically significant reduction in macular oedema for both treatment arms. Previous studies have reported the excellent effect of subthreshold diode laser treatment on DME in terms of improved visual acuity and decreased thickness on OCT without any structural damage in the retinal layers.[14, 28-30,] Pei-Pei *et al.* found that green 532 nm PASCAL subthreshold laser was equally effective in improvement of mean BCVA and CMT as threshold laser grid treatment for patients with DME.[31] Vujosevic *et al.* found no differences in CMT, MV, foveal choroidal thickness, and BCVA between the yellow and infrared subthreshold laser in mild, centre-involving DME with the lowest duty cycle (5%) and fixed power parameters.[32] Luttrull and Sinclair addressed the issue of the ability to treat the fovea directly with a transfoveal subthreshold infrared laser in cases of centre-involving DME and found it to be safe and effective with no evidence of laser-induced macular damage by any imaging means postoperatively and no adverse treatment effects.[13]

In our subgroup analysis, patients with ≥ 400 µm CST at baseline had significantly more reduction in CST at 12 months compared to those patients with baseline CST < 400 µm in both treatment arms. However, this difference was not reflected in the BCVA, with no significant difference seen between both subgroups at 12 months in both treatment arms ($p = 0.83$). Anatomical improvement is not always associated with improvement in functional outcomes.[33-36] Studies by the Diabetic Retinopathy Clinical Research network found only a modest correlation between the change in central foveal point thickness and that in BCVA ($r = 0.44$).[34,35] Soliman *et al.* found that eyes in which more retinal layers were involved at baseline had a poorer functional outcome than eyes in which fewer layers were involved.[37] Mansouri *et al.* reported that subthreshold diode macular laser may be more effective in subjects with mild to moderate DME, as subjects with initial CST ≤ 400 µm responded better in terms of visual acuity gain and decrease in foveal thickness compared to those with central foveal thickness > 400 µm.[38] Valera-Cornejo *et al.* found more improvement in central macular thickness (CMT) in subjects with treatment-naïve, centre-involving DME at 3 months compared to those with refractory DME using yellow 577 nm subthreshold laser photocoagulation ($p = 0.011$).[39] A thicker retina at baseline is reflective of more severe and/or longer-standing disease. The exact cause of this lack of response to subthreshold laser in patients with severe anatomical disease is not clear. Mansouri *et al.* hypothesized that the concentration of cytokines released by the laser stimulation of RPE in severe oedema may be diluted or there might be alterations in distribution of laser energy throughout the retina and RPE due to intra-

and subretinal fluids present in these cases.[38] Perhaps different laser parameters are required in patients with greater oedema. All these studies reiterate that an anatomical reduction of macular oedema is not always followed by an improvement in visual acuity, and the relationship between these two variables is weak.

Another option might be to reduce the macular oedema with anti-VEGF agents or steroids prior to the application of subthreshold laser. Akhalagi showed that using subthreshold diode laser in combination with intravitreal *bevacizumab* can significantly reduce CMT and improve visual acuity in patients with refractory DME.[40] Moisseiev *et al.* reported that subjects treated with a combined therapy of anti-VEGF (ranibizumab) and subthreshold laser needed significantly fewer injections than those treated with ranibizumab alone (2.6 *versus* 9.3 at the end of the follow-up).[41]

In our study, we noted that the patients in the MYL arm had significantly less scarring on slit lamp biomicroscopy (75% *versus* 26.7%) and on FAF (88.9 % *versus* 41.7 %) compared to those in the CGL arm. This is comparable to the findings of Figuera *et al.*, who found a difference of 45% between the two laser treatment modalities.[10] In contrast to this, Luttrull *et al.* found that the incidence of FAF changes in subthreshold 810 nm diode laser ranged from 0% to 8% only, depending on the duty cycle used.[12] Luttrull *et al.* used high-density/low-intensity parameters with a large number of small, densely placed, short-duration laser spots (high density) at a 5% duty cycle (low intensity) to maximize heat dissipation and minimize heat accumulation, thereby reducing the risk of unintended thermal retinal injury.[12] They noted that subthreshold laser at higher retinal irradiance levels (by decreasing wavelength or increasing duty cycle more than 5%) appeared to significantly increase the risk of thermal retinal injury, especially in more darkly pigmented eyes. This could have been the reason for scarring seen in some cases in our MYL arm. Vujosevic *et al.* found no changes indicating damage to the RPE on FAF after subthreshold laser treatment for DME in a prospective study on 50 patients (125-mm spot size, 5% duty cycle of 0.2 seconds, 750 mW power).[11] Lavinsky *et al.* did a detailed analysis of retinal structures changes under certain fluence reductions and concluded that 30% of threshold energy does not create any tissue defects.[42] Chhablani *et al.* reported that the 15% duty cycle setting seems to achieve the highest ETDRS letter gain and largest decrease in volume compared to the 5% duty cycle parameters using 577 nm subthreshold laser with power reduced to 30% of continuous wave laser.[43] Our study was performed in 2011–2012, before the publication of these studies. We followed an earlier protocol used by Figuera *et al.*[10] for the subthreshold laser, with 300 ms and double the power used for the test burn. With the benefit of hindsight, reducing the exposure to 100 ms and careful power titration with 15 % duty cycle to achieve 30% of threshold energy would probably have reduced the scarring even further. The main challenge faced by ophthalmologists while using the subthreshold laser is difficulty in titration and documentation of treatment, as there is no actual endpoint, such as a visible burn. Subthreshold laser parameters and titration protocols vary significantly between studies and there is no strong recommenda-

*Table 5.* Protocols used for subthreshold micropulse laser in different studies for diabetic macular oedema

| Author (Year) | Spot size (μm) | Duty cycle (%) | Duration of exposure (ms) | Power |
|---|---|---|---|---|
| Lutrull *et al.* (2005)[9] | 125 | 5 | 300 | Fixed at 750mW |
| Figuera *et al.* (2009)[10] | 125 | 15 | 300 | CWL power doubled |
| Vujosevic *et al.* (2010)[11] | 125 | 5 | 200 | 750mW (fixed) with infrared laser |
| Lavinsky *et al.* (2011)[14] | 125 | 15 | 300 | CWL power increased by 20% |
| Lutrull *et al.* (2014)[13]<br>2 protocols | 125<br>125 | 5<br>5 | 300<br>300 | Fixed power of 950mW<br>Fixed power of 780mW |
| Mansouri *et al.* (2014)[38] | 125 | 5 | 300 | Fixed power of 950 mW |
| Vujosevic *et al.* (2015)[32]<br>2 protocols | 100<br>125 | 5<br>5 | 200<br>200 | 250mW with yellow laser (fixed)<br>750 Mw with infrared laser (fixed) |
| Chhablani *et al.* (2018)[43]<br>2 protocols | 100<br>100 | 5<br>15 | 100<br>100 | Power titrated to 30% of CWL |
| Akhlaghi *et al.* (2019)[40] | 200 | 5 | NA | Titrated to four times the CWL power |
| Bougatsou *et al.* (2020)[28] | 100 | 15 | 100 | Titrated to double the CWL power |
| Valera-Cornejo *et al.* (2021)[39] | 100–150 | 5 | 200 | Power reduced to 50% of CWL |

CWL: continuous-wave laser

tion so far about ideal parameters for DME treatment. Some authors advocate fixed parameters while others prefer varied methods of titration. The different protocols used in various studies are listed in Table 5.

The strengths of this study are it is a single-centre, prospective, randomized, and controlled nature standardized measurements and laser protocol, and adequate follow-up period of 12 months. All the patients were treated by only two ophthalmologists so as to reduce the bias in difference in technique. The weaknesses of this study were its small sample size and lack of functional visual assessment such as

microperimetry and contrast sensitivity. The patients in our study had poor diabetic control, which also makes the management of DME harder. However, this situation reflects the real-life challenging scenario faced by many ophthalmologists treating DME.

## Conclusion

In conclusion, our results revealed that MYL is an effective, safe, and patient-friendly treatment option for CSME, with improvement in BCVA, reduction in macular thickness, and less scarring after treatment at 12 months.

## Declarations

**Ethics approval and consent to participate**
This study was a prospective, randomized, controlled clinical trial performed at the Eye Clinic of University of Malaya Medical Centre (UMMC) from August 2009 to December 2011. The study was approved by the UMMC Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients who participated in the study. This study was listed on www.clinicaltrials.gov, under identifier NCT01045239.

**Competing interests**
The authors declare they have no competing interests.

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# Characteristics of polypoidal choroidal vasculopathy in the Malaysian population

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## Abstract

*Introduction:* Polypoidal choroidal vasculopathy (PCV) is a distinct clinical entity, characterized by focal hyperfluorescence in the early phase of indocyanine green angiography (ICGA), with or without its associated branching vascular network (BVN).
*Purpose:* To report the angiographic characteristics of PCV on ICGA in presumed PCV patients.
*Study design:* Descriptive cross-sectional study.
*Materials and methods:* This study involved 36 suspected PCV patients who attended the Ophthalmology Clinic, Universiti Kebangsaan Malaysia Medical Centre from June 1, 2012 to May 31, 2013. All patients underwent complete ophthalmologic examination including colour fundus photography, ICGA, and fundus fluorescein angiography. ICGA images of confirmed PCV patients were analysed.
*Results:* Twenty-five out of 36 eyes (69.4%) were diagnosed to have PCV based on ICGA. Mean age of confirmed PCV patients was 66.4 ± 8.42 years, with predominance of males (*n* = 17) and Chinese ethnicity (*n* = 19). Best-corrected visual acuity (BCVA) was between 6/6 and 6/18 in 64%. All 25 patients had unilateral disease. Average size of PCV lesions was 1461.4 ± 864.4 µm. The lesions were mostly concentrated in the extrafoveal region (*n* = 15, 60%). Lesion formation was cluster

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in 56% (*n* = 14), single in 32% (*n* = 8), string in 4% (*n* = 1), and combination in 8% (*n* = 2). The majority involved a single discrete area. Polyp pulsation was detected in six eyes, while seven eyes revealed nodular hyperfluorescence when viewed stereoscopically. BVN was evident in 56% (*n* = 14). Fifteen eyes demonstrated the hypofluorescent halo, while no hyperfluorescent ring was seen in this study population. Late geographical hyperfluorescence (LGH) was noted in seven eyes (28%). There was no significant association between the morphological characteristics of PCV, *i.e.*, size of lesion, location, formation, discrete area involved, and LGH with BCVA.
*Conclusion:* The demographic, clinical, and angiographic features observed in this study were in agreement with other previously published Asian studies. However, we found no association between the morphological characteristics of PCV with BCVA.

*Keywords:* branching vascular network, focal hyperfluorescence, indocyanine green angiography, polypoidal choroidal vasculopathy

# Abstrak

*Pengenalan:* Penyakit "polypoidal choroidal vasculopathy" (PCV) merupakan entiti klinikal yang unik, bercirikan hiperfluoresen tertumpu yang dilihat pada fasa awal angiografi "indocyanine green" (ICGA), dengan atau tanpa rangkaian vaskular bercabang ("branching vascular network" (BVN)).
*Tujuan:* Untuk melaporkan ciri-ciri penyakit PCV dengan mengkaji imej-imej ICGA pesakit yang disyaki menghidapi PCV.
*Reka bentuk kajian:* Kajian keratan rentas deskriptif.
*Metodologi:* Kajian ini bermula dari 1 Jun 2012 hingga 31 Mei 2013 dan melibatkan 36 orang pesakit yang disyaki menghidapi PCV dari Klinik Oftalmologi, Pusat Perubatan Universiti Kebangsaan Malaysia. Para pesakit menjalani pemeriksaan mata komprehensif, termasuk pengambilan gambar fundus, ICGA dan angiografi "fundus fluorescein". Imej-imej ICGA yang telah disahkan sebagai penyakit PCV telah dianalisa.
*Keputusan:* Dua puluh lima dari 36 mata (69.4%) disahkan sebagai PCV berdasarkan analisa ICGA. Purata umur ialah 66.4 ± 8.42 tahun, dengan majoritinya lelaki (*n* = 17) dan kaum Cina (*n* = 19). 64% mempunyai tahap penglihatan 6/6 sehingga 6/18. Kesemua 25 pesakit mengalami PCV pada sebelah mata sahaja. Purata saiz PCV ialah 1461.4 ± 864.4 μm. Kebanyakan PCV ditemui pada kawasan "extrafoveal" (*n* = 15, 60%). Pembentukan PCV adalah berkelompok 56% (*n* = 14), tunggal 32% (n = 8), menyerupai "tali" 4% (*n* = 1) dan kombinasi 8% (*n* = 2). Majoriti PCV ditemui di dalam satu kawasan sahaja. 6 mata dikesan mempunyai polip berdenyut, sementara 7 mata mempamerkan "nodular hyperfluorescence" apabila

dilihat secara stereoskopik. BVN jelas kelihatan pada 56% mata ($n$ = 14). 15 mata menunjukkan "hypofluorescent halo", sementara tiada "hyperfluorescent ring" dikesan. "Late geographical hyperfluorescence" (LGH) diperhatikan pada 7 mata (28%).

Tiada kaitan yang signifikan di antara ciri-ciri morfologi penyakit PCV seperti saiz lesi, lokasi, pembentukan, kawasan yang terlibat, LGH dengan tahap penglihatan.

*Kesimpulan:* Data demografi, ciri klinikal serta ciri-ciri ICGA di dalam kajian ini mempunyai persamaan dengan kajian-kajian terdahulu yang melibatkan penduduk negara-negara Asia yang lain. Ciri-ciri morfologi PCV tidak mempengaruhi tahap penglihatan.

*Kata kekunci:* rangkaian vaskular bercabang, fokus hiperfluoresen, angiografi "indocyanine green", "polypoidal choroidal vasculopathy"

## Introduction

Polypoidal choroidal vasculopathy (PCV) is a distinct clinical entity characterized by focal hyperfluorescence in the early phase of indocyanine green angiography (ICGA), with or without its associated branching vascular network (BVN).[1] The clinical findings of PCV vary considerably, thus raising a diagnostic dilemma. There is significant overlap between the retinal manifestations of this disease with exudative age-related macular degeneration (AMD).[2-4] Some authorities consider PCV as a variant of neovascular AMD.[5] However, the natural history and visual prognosis of PCV are more favourable.[6-8] On the other hand, others regard it as a different disease entirely.[6,9] Published studies from Asian countries quote that the proportion of PCV among eyes with exudative AMD ranges from 9.3–55%,[5,9-12] while data from Caucasian populations revealed that the PCV prevalence among exudative AMD patients is 7.8–12%.[4,13-15]

The knowledge on PCV is rapidly evolving as the work is still ongoing. Based on the fact that PCV may mimic other acquired macular disorders, this study was undertaken to describe the diverse clinical and angiographic manifestations of this peculiar disease, specifically in presumed PCV patients attending the Ophthalmology Clinic, Universiti Kebangsaan Malaysia (UKM) Medical Centre. It is imperative to clarify the demographic features of PCV, together with its clinical and angiographic characteristics, so that the optimal management can be established for the patients.

The aims of this study were to determine the prevalence of PCV in presumed PCV patients, to describe the angiographic characteristics in confirmed PCV patients, and to determine the association between the morphological characteristics of PCV and best-corrected visual acuity (BCVA).

## Materials and methods

This cross-sectional study was conducted from June 1, 2012 to May 31, 2013 at the Ophthalmology Clinic, UKM Medical Centre, Kuala Lumpur, Malaysia. Ethics approval from the Research and Ethics Committee, Faculty of Medicine, Universiti Kebangsaan Malaysia (FF-156-2012) and National Medical Research Register of the Ministry of Health Malaysia were obtained prior to commencement of the study. The study followed the guidelines set in the Malaysian Good Clinical Practice (2nd edition, January 2004) and was conducted in accordance to the principles of the Declaration of Helsinki.

The inclusion criteria for the study were patients ≥ 50 years old with suspected PCV features on fundoscopy and fundoscopic examination revealing serosanguineous maculopathy with one of the distinctive features of visible, orange-red subretinal nodules, serous, serosanguineous, or notched retinal pigment epithelial detachment (PED), chronic or multifocal central serous chorioretinopathy (CSCR), massive submacular haemorrhage, or breakthrough bleeding into the vitreous. Patients were excluded from the study if they had diabetic maculopathy, maculopathy secondary to central or branch retinal vein occlusion, pathological myopia, angioid streaks, presumed ocular histoplasmosis syndrome, significant media opacities preventing adequate fundus examination and photography, history of ocular trauma, previous panretinal laser photocoagulation, known allergy towards sodium fluorescein or indocyanine green dyes, and did not consent to ICGA and fundus fluorescein angiography (FFA).

Patients who fulfilled the inclusion criteria were identified and recruited into the study. The nature and purpose of the study were explained in detail to all participants by the investigator and provided in an information sheet. Informed consent was obtained from those who agreed to participate. Consecutive, universal sampling of patients was employed in this study.

A digital colour fundus photograph of the macular region (50 angles of coverage) was acquired using a Topcon TRC-50DX (Type IA) retinal camera (Topcon, Tokyo, Japan). Optical coherence tomography (OCT) was performed using a Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany).

For the ICGA, 25 mg of indocyanine green molecules dissolved in 5 ml of sterile water for injection was injected into the cubital vein. Dynamic high-speed ICGA using the Heidelberg Retinal Angiograph 2 (HRA2) (Heidelberg Engineering, Dossenheim, Germany) was recorded for the first 30 seconds, while still frames were acquired at 1, 2, 5, 10, 15, and 30 minutes. Stereo pairs were also captured.

FFA was also performed using the HRA2 after completion of ICGA. The procedure required the intravenous injection of 5 ml of 10% sodium fluorescein solution through the existing brannula. Angiography commenced in 10 to 12 seconds, following quick (less than 6 seconds) fluorescein injection. A video during the filling phase was captured. Images of the macula were further obtained at approx-

imately 30, 60, 90, and 180 seconds post-injection. Late-phase photos were taken between 5 and 10 minutes post-injection.

The angiograms were evaluated independently by a medical retina specialist (WHS) and the investigator (RAN). Once the diagnosis of PCV was confirmed, the ICGA images were analysed by the investigator. The lesions were analysed according to size of polyp, location, formation, and number of discrete polyp areas. After this preliminary analysis, two medical retina specialists (WHS and ALLS) reviewed the angiograms again to correlate the ICGA findings with the FFA findings. The following features were noted on FFA: blocked fluorescence and choroidal neovascular membrane (CNV) characteristics; namely, classic, predominantly classic, minimally classic, and occult.[16] The following features were noted on ICGA: interconnecting channels (ICC), BVN with late leakage, and absence of leakage. ICC was defined as a criss-crossed network which fills up simultaneously during the choroidal phase and has no specific direction of flow or point of origin.[17] BVN was defined as a vascular network that shows a unidirectional flow or a point of origin which fans out to the periphery to supply terminal polyps.[17]

PCV is defined as the presence of hyperfluorescence or hot spot (polyp) occurring early in the ICGA which persisted into the late stage, with at least one of the clinical or angiographic criteria being met (a dark halo surrounding it, pulsation in the polyp, presence of ICC or BVN, nodular appearance on stereoscopic view, orange subretinal nodules on colour fundus photograph, or presence of massive submacular haemorrhage of at least four disc areas).[1] Presence or absence of dye leakage was documented, and the source of leakage —either from BVN, polyps, or both— was identified.

To minimize errors, all funduscopic examinations were performed by the principal investigator (RAN); digital colour fundus photography, OCT, ICGA, and FFA were performed by a single trained staff; and independent interpretation of the angiograms were conducted by the investigator and a medical retina specialist.

The raw data were tabulated using Microsoft Office Excel 2007. The keyed in data were checked for entry errors and inconsistencies. The data was analysed using Statistical Package for Social Sciences (SPSS) Statistics 22. Kolmogorov-Smirnov test was used to test the normality of the distribution. The independent samples T-test was employed to analyse continuous variables against categorical data. Pearson's Chi-square test was utilised to look for any association between morphological characteristics and BCVA. A *P*-value of less than 0.05 was considered significant. Correlation analyses were performed to look for correlations between the CNV type (classic and occult) and blocked fluorescence seen on FFA, and late leakage from the BVN on ICGA with PCV.

*Table 1.* Characteristics of visual symptoms

| | **Number of patients, *n* = 36 (%)** |
|---|---|
| Eye affected | |
| Right | 22 (61.1) |
| Left | 14 (38.9) |
| Symptoms | |
| Asymptomatic | 8 (22.2) |
| Blurring of vision | 14 (38.9) |
| Central scotoma | 7 (19.4) |
| Metamorphopsia | 7 (19.4) |
| Floaters | 0 (0.0) |
| Duration | |
| < 1 month | 4 (14.3) |
| 1–12 months | 17 (60.7) |
| > 12 months | 7 (25.0) |
| Best-corrected visual acuity | |
| 6/6–6/18 | 24 (6.7) |
| < 6/18–6/60 | 6 (16.7) |
| < 6/60 | 6 (16.7) |

## Results

From June 1, 2012 to May, 31 2013, 36 patients (36 eyes) who fulfilled the study inclusion criteria were included in the study (Table 1); from this group only 25 eyes had confirmed PCV. The age of the PCV patients ranged from 50 to 84 years old, with a mean age of 66.4 ± 8.42 years. Seventeen (68.0%) were men and 8 (32.0%) were women. Chinese ethnicity was predominant in this group with 76.0%, while 48.0% were active and ex-smokers. Sixteen (64.0%) patients had a BCVA between 6/6 and 6/18, with the remainder having a BCVA worse than 6/18 (Table 2).

The non-PCV patients were diagnosed with exudative AMD ($n$ = 6), retinal angiomatous proliferation (RAP) ($n$ = 1), CSCR ($n$ = 1), PED ($n$ = 1), and diabetic macular oedema ($n$ = 1). One patient had a massive subretinal bleed, rendering the ICGA and FFA images inconclusive.

The right eye was affected in 60% of the PCV group. Forty percent complained of blurred vision, while 20% noted a central scotoma, another 20% had metamorphopsia, and the rest were asymptomatic. No patients had floaters. The duration of symptoms ranged from 1 week to 5 years.

A total of 12 eyes had PED: 3 haemorrhagic, 3 large, and the remainder serous. Ten out of 16 eyes had exudation on fundoscopy. Subretinal nodules were observed in

*Table 2.* Demographic data of PCV patients

| **Characteristics** | ***n* (%)** |
|---|---|
| Mean age (years ± SD) | 66.4 ± 8.42 |
| Gender | |
| Female | 8 (32.0) |
| Male | 17 (68.0) |
| Ethnicity | |
| Malay | 6 (24.0) |
| Chinese | 19 (76.0) |
| Smoking status | |
| Active | 10 (40.0) |
| Ex-smoker | 2 (8.0) |
| Non-smoker | 13 (52.0) |
| Best-corrected visual acuity | |
| 6/6–6/18 | 16 (64.0) |
| < 6/18 | 9 (36.0) |

only two eyes, while only one eye presented with massive submacular haemorrhage. Nine eyes were noted to have subretinal/subretinal pigment epithelium (RPE) fluid and subretinal bleed. Only one eye had an ipsilateral macular scar. Age-related maculopathy (ARM) was documented in 14 fellow eyes (Table 3).

The size of PCV lesions measured as the greatest linear dimension (GLD) ranged from 223 to 3625 µm, with an average mean of 1461.4 ± 864.4 µm. More than half the PCV lesions ($n$ = 15, 60%) were concentrated in the extrafoveal region, the majority of which involved a single discrete area. As for the formation of lesions, 56% ($n$ = 14) were in clusters, followed by single formation at 32%. Only six eyes were found to have pulsating polyps on dynamic ICGA, while nodular hyperfluorescence when viewed stereoscopically was only seen in seven cases. BVN was evident in 56% ($n$ = 14). Fifteen patients demonstrated the hypofluorescent halo surrounding the polyp, while no hyperfluorescent ring was seen in any case. PED was present in seven (28%) patients. Late geographical hyperfluorescence (LGH) was demonstrated in seven eyes (28%) (Table 4).

There was no significant difference noted in the mean size of PCV lesions between the two BCVA groups, $P$ = 0.232 (Table 5). Further analysis of PCV lesion characteristics did not reveal any statistically significant association between BCVA and morphological characteristics of said lesions, $P$ > 0.05 (Tables 6–9).

Twelve (48%) of the PCV patients were active smokers or ex-smokers. There was no statistically significant association found between smoking and PCV (Chi-square test, $P$ = 0.271).

*Table 3.* Retinal manifestations of PCV patients

| **Funduscopic findings** | **Number of eyes, *n*** |
|---|---|
| Subretinal nodule | 2 |
| PED<br>Large<br>Serous<br>Haemorrhagic | 12<br>3<br>6<br>3 |
| Massive submacular haemorrhage | 1 |
| Exudation | 10 |
| Subretinal bleed | 5 |
| Subretinal/sub-RPE fluid | 4 |
| Intraretinal haemorrhage | 3 |
| Drusen<br>Hard<br>Soft | <br>4<br>1 |
| Macular scar | 1 |
| ARM in fellow eye | 14 |

PCV: polypoidal choroidal vasculopathy; PED: retinal pigment epithelium detachment; RPE: retinal pigment epithelium; ARM: age-related maculopathy

*Table 5.* Association between BCVA and size of PCV lesions

| **BCVA** | **Size of PCV lesions (mean (SD)) (µm)** | ***P*-value** |
|---|---|---|
| 6/6–6/18 | 1308.14 (770.58) | 0.232 [a] |
| < 6/18–CF | 1783.2 (1000.61) | |

BCVA: best-corrected visual acuity; PCV: polypoidal choroidal vasculopathy; CF: counting fingers

[a]Independent samples T-test, $P < 0.05$

*Table 4.* Indocyanine green angiography characteristics in confirmed PCV patients (*n* = 25)

| ICGA characteristics | Frequency | Percentage (%) |
|---|---|---|
| Location | | |
| Subfoveal | | |
| Juxtafoveal | 6 | 23 |
| Extrafoveal | 1 | 4 |
| Peripapillary | 15 | 60 |
| Combination | 2 | 8 |
| | 1 | 4 |
| Area involved | | |
| Single | 25 | 80 |
| Multiple | 5 | 20 |
| Formation | | |
| Single | 8 | 32 |
| Cluster | 14 | 56 |
| String | 1 | 4 |
| Combination | 2 | 8 |
| Pulsation of polyp | 6 | 24 |
| Leakage on ICGA | 9 | 36 |
| Polyp | 5 | |
| BVN | 1 | |
| Both | 3 | |
| Nodular lesion | 7 | 28 |
| BVN | 14 | 56 |
| Hypofluorescent halo | 15 | 60 |
| Hyperfluorescent ring | 0 | 0 |
| PED | 7 | 28 |
| LGH | 7 | 28 |

PCV: polypoidal choroidal vasculopathy; ICGA: indocyanine green angiography; BVN: branching vascular network PED: retinal pigment epithelium detachment; LGH: late geographical hyperfluorescence

*Table 6.* Association between BCVA and location of PCV lesions

| BCVA | Subfoveal, *n* (%) | Juxtafoveal, *n* (%) | Extrafoveal, *n* (%) | P/papillary, *n* (%) | Combo, *n* (%) | *P*-value |
|---|---|---|---|---|---|---|
| 6/6–6/18 | 3 (18.75) | 1 (6.25) | 11 (68.75) | 1 (6.25) | 0 (0.00) | 0.465[a] |
| < 6/18–CF | 3 (33.33) | 0 (0.00) | 4 (44.44) | 1 (11.11) | 1 (11.11) | |

BCVA: best-corrected visual acuity; PCV: polypoidal choroidal vasculopathy; CF: counting fingers
[a]Pearson Chi-square test, $P < 0.05$

*Table 7.* Association between BCVA and formation of PCV lesions

| BCVA | Single, *n* (%) | Cluster, *n* (%) | String, *n* (%) | Combo, *n* (%) | *P*-value |
|---|---|---|---|---|---|
| 6/6–6/18 | 6 (37.50) | 8 (50.00) | 1 (6.25) | 1 (6.25) | 0.697[a] |
| < 6/18–CF | 2 (22.22) | 6 (66.67) | 0 (0.00) | 1 (11.11) | |

BCVA: best-corrected visual acuity; PCV: polypoidal choroidal vasculopathy; CF: counting fingers
[a]Pearson Chi-square test, $P < 0.05$

*Table 8.* Association between BCVA and number of discrete PCV areas

| BCVA | Single, *n* (%) | Multiple, *n* (%) | *P*-value |
|---|---|---|---|
| 6/6–6/18 | 12 (75.00) | 4 (25.00) | 0.405 [a] |
| < 6/18–CF | 8 (88.89) | 1 (11.11) | |

BCVA: best-corrected visual acuity; PCV: polypoidal choroidal vasculopathy; CF: counting fingers
[a]Pearson Chi-square test, $P < 0.05$

*Table 9.* Association between BCVA and late geographical hyperfluorescence (LGH)

| BCVA | LGH present, *n* (%) | No LGH, *n* (%) | *P*-value |
|---|---|---|---|
| 6/6–6/18 | 5 (31.25) | 11 (68.75) | 0.629 [a] |
| < 6/18–CF | 2 (22.22) | 7 (77.78) | |

BCVA: best-corrected visual acuity; LGH: late geographical hyperfluorescence; CF: counting fingers
[a]Pearson Chi-square test, $P < 0.05$

*Table 10.* FFA findings in PCV and non-PCV patients

| FFA findings | PCV, *n* (%) | Non-PCV, *n* (%) |
|---|---|---|
| Blocked fluorescence | 4 (16.0) | 2 (data not available for 8 eyes) |
| Classic CNV lesion | 1 (4.0) | 0 (0.0) |
| Predominantly classic CNV lesion | 3 (12.0) | 2 (28.6) |
| Minimally classic CNV lesion | 9 (36.0) | 1 (14.3) |
| Occult CNV lesion | 11 (44.0) | 4 (57.1) |

FFA: fundus fluorescein angiography; PCV: polypoidal choroidal vasculopathy; CNV: choroidal neovascularization

Table 10 documents the type of CNV found in PCV patients on FFA. The majority of PCV patients show minimally classic and occult CNV lesions on FFA. We found that 11 (44%) and 14 (56%) of PCV patients had ICC and BVN on their ICGA images, respectively. Eight (57.1%) out of 14 eyes with BVN demonstrated late leakage on FFA. In particular, the type of CNV on FFA with the ICGA features of BVN with late leakage was investigated. There was no significant correlation between the two parameters, (correlation coefficient, ρ = -0.39, $P$ = 0.15). There was also no significant association as tested with logistic regression analysis between the two variables, $p$ = 0.154.

## Discussion

The prevalence of presumed PCV in our study is 69.4%. This is high compared to previous Asian studies, which quote the proportion of PCV in patients with features of exudative AMD in the range of 9.3–55%.[5,6,10-12] On the other hand, the prevalence of exudative AMD in Caucasians ranges from 7.8–12%.[4,13,15] Our prevalence is high owing to the fact that we included patients who we presumed to have PCV. As a matter of fact, the prevalence should be even higher than our current results, as we included patients who presented with known clinical features of PCV, namely, presence of orange subretinal nodule, serous, serosanguineous, or notched PED, massive submacular haemorrhage, and CSCR-like features.[16] The less than expected prevalence highlights the fact that other acquired macular diseases may mimic PCV.

The average mean age of PCV patients in our study population was 66.96 years, which is similar to other studies conducted in Asian countries. Men were more likely to be affected than women by a 2:1 ratio, which also seems to be in accordance to other studies carried out in Japan, Korea, and China.[5-6,12] In whites, there is female predominance.[9] There was a majority of Chinese patients in our study, which can be attributed to the fact that Cheras and areas nearby Kuala Lumpur, catered by our institution, are densely populated by this ethnic group.

The presence of orange subretinal nodular structures associated with an adjacent serous PED or a neurosensory detachment, subretinal bleed, and lipid exudation is the clinical hallmark of PCV.[1] Features typical of PCV found in our study in decreased frequency were lipid exudation, serous PED, large PED, subretinal bleed, subretinal nodule, and massive submacular haemorrhage.

Soft drusen were only noted in one affected and two fellow eyes, indicating that they are relatively rare in PCV. This finding is supported by another study.[5] There was only one eye affected by an ipsilateral non-disciform macular scar in the confirmed PCV patients. Disciform scarring is believed to be uncommon in PCV.[17] Poor vision in our patients was mainly caused by massive submacular haemorrhage and exudation involving the macula.

PCV is thought to be a bilateral disease, with the fellow eye eventually developing similar lesions.[18] Our study failed to reveal bilaterality as all our patients had unilateral disease. This may be attributed to the small sample size of our study.

The retinal manifestations of PCV observed in our study were like those of AMD patients; this is supported by other previously published studies.[4] It was no surprise that six patients in our study were eventually diagnosed with exudative AMD. PCV is regarded as having a low incidence of subretinal fibrovascular proliferation and known to progress slowly.[19] These factors confer a more favourable visual prognosis compared to exudative AMD patients. It is vital to distinguish PCV from AMD as there are significant differences in the patients' profile, natural course, treatment, and visual outcome. High index of suspicion is required when neovascular AMD patients do not respond well to anti-vascular endothelial growth factor injections, as they might have been misdiagnosed or there may be coexisting PCV.[20]

One non-PCV patient presented with multiple intraretinal haemorrhages associated with macular oedema and a scar. Clinically, it was consistent with exudative AMD. A diagnosis of RAP, a form of CNV, was finally made. RAP lesions are sometimes seen as focal areas of hyperfluorescence or "hot spots" on ICGA, and during the mid and late phases, these lesions become markedly hyperfluorescent as the dye leaks into the intraretinal spaces.[21] In this patient, the abnormal retinal vessel was seen to turn sharply into the choroid. However, there was no hot spot or leakage noted.

One patient was observed to have features of chronic CSCR. Usually, the diagnosis of CSCR can be made with little difficulty. Patients are typically adults with "type-A" behaviour pattern, presenting with an exudative detachment of the neurosensory retina, frequently with associated multiple serous PEDs and patches of RPE atrophy.[22] However, with prolonged exudation, as in this case, a variety of RPE changes can develop that may lead to establishing the correct diagnosis a bit tricky. Moreover, there have been reports of macular variants of PCV with similar clinical and FFA features resembling CSCR.[17,23] In our patient, ICGA ruled out PCV, while FFA demonstrated pinpoint leaks confirming CSCR.

All the previously mentioned cases emphasize the fact that other macular disorders can mimic PCV. Accurate diagnosis is thus imperative for patients to be optimally managed.

In this study, the size of PCV lesions measured as the GLD ranged from 223 to 3625 µm, with an average mean of 1461.4 ± 864.4 1 µm. The smallest value of 223 µm corresponded to an individual polyp without any BVN, while the largest value of 3625 µm corresponded to an extrafoveal cluster of polyps with extensive BVN complex. With such a large area involved, it was expected that this patient's BCVA would be poor. Surprisingly enough, it was good at 6/12 due to resolving subretinal fluid. There was no ICGA leakage, but leakage was evident on FFA. It is imperative to treat this lesion as clinically active. If left untreated, it tends to recur and thus

carries a worse visual prognosis.

The main location for PCV lesions observed in our study was the extrafoveal area. This finding is similar to that of a study conducted by Cackett on Chinese patients affected by PCV in Singapore.[24] The most frequently noted formation was cluster, followed by single. Uyama *et al.* reported that grape-like clusters of polyps were associated with marked haemorrhage and leakage, with subsequent severe visual loss.[25] PCV lesions in this study were found to involve more single discrete areas than multiple areas. This may be translated further to less aggressive treatment required and potentially good visual outcome.

Polyp pulsation was detected in six eyes. The presence of typical subretinal nodular hyperfluorescence when viewed stereoscopically in our study was noted in only seven eyes (28%), as compared to over 80% in definite PCV eyes.[1] Perhaps the imaging technique used was inferior to the other study. BVN was elucidated in only 14 eyes (56%). Our detection rate was lower compared to 75% of demonstrated BVN in a previous study.[1] Our finding has to be taken into consideration in the determination of laser treatment spot size used for photodynamic therapy (PDT) as initial treatment is usually targeted towards covering the polyp and its associated BVN complex. Failure to incorporate the BVN during PDT may result in persistent or recurrent leakage, thus affecting the visual prognosis.

In our study, 60% of polyps were observed to have a hypofluorescent halo, which is thought to arise from an active polyp. No hyperfluorescent ring was documented in this study. This may be due to inadequate staining of the polyp wall, thus affecting detection of the ring.

LGH was documented in 28% of patients. Kang *et al.* reported that persistence of LGH after PDT was associated with polyp recurrence.[26] All of our patients were treatment-naïve. Hence, this finding may represent another important angiographic manifestation of PCV lesions. If this holds true, then it is crucial to include the area of LGH in the determination of laser treatment spot size during PDT, so that recurrence can be avoided.

One publication reported that eyes with cluster of grape-like polyps had an increased risk of severe visual loss.[25] Other authors have hypothesized that eyes with larger sizes of PCV lesions and involvement of multiple areas carry a poor prognosis.[1]

Some authorities consider that PCV is a variant of neovascular AMD, and smoking has been well implicated in the pathogenesis of the latter disease. Smoking may impair choroidal blood flow, and thus promote ischaemia, hypoxia, and micro-infarctions. All these can cause increased susceptibility of the macula to oxidative damages and degenerative changes.[30] However, we were unable to establish an association between smoking and PCV due to the small sample size.

Knowledge of the characteristics of PCV is vital for proper diagnosis and precise management of this peculiar disease. It is fundamental for the ICGA differences of PCV to be delineated, as this might prove useful as a prognostic indicator. Since this

study was previously conducted when PCV was a relatively new ocular disease and with the introduction of new terminology such as ICC to describe the disease, we decided to review the angiographic findings again and attempted to correlate the FFA and ICGA findings.

A Japanese study by Maruko *et al.* found that 11.3% of 203 eyes with PCV showed classic CNV lesions.[5] In these cases, 1.5%, 9.8%, and 88.7% had predominantly classic CNV, minimally classic CNV and occult CNV, respectively.[5] Most of their patients had minimally classic or occult CNV on FFA, which is similar to our findings. Occult CNV or type 1 CNV neovascular complex is mainly found below the RPE. Hence, occult CNV is commonly seen in PCV cases. One patient from our study cohort showed pure classic CNV appearance on FFA. Tamura *et al.* studied PCV eyes with classic CNV and found that the presence of classic CNV could be due to the presence of type 2 CNV or pure fibrinous subretinal material seen on OCT.[29] Leaking polypoidal lesions potentially lead to subretinal fibrinous exudation, which could also mimic classic CNV picture in FFA. Among PCV eyes with classic CNV, visual prognosis was found to be poorer.[29]

Tan *et al.* classified the ICGA lesions of PCV into 3 subtypes: type A, B, and C. In type A lesions, polyps were supplied by ICC, whereas type B and C lesions typically show a BVN that exhibits unidirectional blood flow from a specific point towards the polyps. The differentiating feature between these two lesions is the presence of late leakage in FFA for type C PCV.[17] This classification has become a useful tool for prognostication of PCV eyes. Type A lesions have the best visual outcome among the three subtypes, while type C lesions have the highest rate of moderate visual loss at 5 years.[17,31] It was reported that 53.3% ($n$ = 26) of eyes in their Singapore cohort showed type C PCV vascular subtypes.[17] Type A and B subtypes were 22.4% ($n$ = 24) and 24.3% ($n$ = 26), respectively.[17] Contrarily, EVEREST study I demonstrated that type B PCV was a predominant feature in ICGA with 50% ($n$ = 27).[31] Fifteen percent ($n$ = 8) had type A while 35.2% ($n$ = 19) had type C lesions.[31] In our study, 14 (56%) patients showed BVN on their ICGA; eight (57.1%) out of these 14 eyes with BVN demonstrated late leakage on FFA. Our study was a descriptive cross-sectional study, therefore we were unable to demonstrate visual acuity changes over time. A longitudinal prospective study is needed to determine the association between visual acuity loss and BVN with late leakage.

The main drawback of this study is its small sample size. Other ethnic groups such as Malays and Indians were not well represented, which can lead to potential bias. OCT findings were not included in the analysis. Also, given the duration available for the study, we were unable to review the visual acuity outcome of the patients after a number of years in order to correlate with the clinical and angiographic findings. This should be the subject of future studies.

Knowledge of the characteristics of PCV is vital for the proper diagnosis and precise management of this peculiar disease. It is fundamental for the ICGA differences of PCV to be delineated, as this might prove useful as a prognostic

indicator. In conclusion, the diagnosis of PCV can be made with a high level of certainty when the clinical hallmark features of this disease are present. ICGA is the gold standard in clinching the correct diagnosis. Nevertheless, it must be borne in mind that other acquired macular diseases such as exudative AMD and CSCR may present as PCV, thus complicating the diagnosis and raising the possibility of erroneous treatment. The demographic, clinical and angiographic features observed in this study are in accordance with other previously published Asian studies. However, this study did not demonstrate an association between the morphological characteristics of PCV, namely, the size of lesions, location, formation, and number of discrete areas involved, with BCVA.

## Declarations

**Ethics approval and consent to participate**
Ethics approval from the Research and Ethics Committee, Faculty of Medicine, University Kebangsaan Malaysia (FF-156-2012) and National Medical Research Register of the Ministry of Health Malaysia were obtained prior to commencement of the study. The study followed the guidelines set in the Malaysian Good Clinical Practice (2nd edition, January 2004) and was conducted in accordance to the principles of the Declaration of Helsinki.

**Competing interests**
None to declare.

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*Case series*
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# Case series of clinical features in siblings with X-linked juvenile retinoschisis

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## Abstract

X-linked juvenile retinochisis (XLRS) is a rare inherited bilateral vitreoretinal dystrophy which usually affects males early in life. We describe the clinical findings, outcome, and challenges in treatment of three siblings diagnosed with XLRS. Three siblings with ages ranging from 5 to 9 years old presented with reduced visual acuity (VA) and posterior segment showing varying degrees of vitreous veil and spoke-wheel maculopathy. Optical coherence tomography (OCT) of the macula was performed, revealing retinoschisis in all eyes. All three siblings were diagnosed with XLRS and were started on topical brinzolamide twice daily. OCT was repeated at 6 months and 18 months. At 18 months, three eyes showed stable VA and three eyes showed improved in VA. One out of the three eyes with stable VA showed improved retinoschisis while the other two eyes showed worsening retinoschisis. On the other hand, one out of the three eyes with improved VA had improved retinoschisis and the other two had worsening retinoschisis. We demonstrated that the VA of patients with retinoschisis is not directly proportional to the degree of splitting of the neurosensory retina. Retinoschisis treatment is challenging, as there is no one proven effective treatment up to date.

*Keywords:* macular degeneration, siblings, visual acuity, X-linked juvenile retinoschisis

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# Abstrak

Retinoschisis juvana 'X-linked' ("X-linked juvenile retinoschisis" [XLRS]) adalah sejenis penyakit keturunan distrofi retina yang jarang ditemui dan sering melibatkan jejaka pada usia muda. Di sini kami menerangkan manifestasi klinikal dan cabaran dalam rawatan tiga adik beradik yang dikenalpasti mendapat penyakit XLRS. Tiga adik beradik yang usia antara 5 hingga 9 tahun mengadu kurang ketajaman penglihatan. Pemeriksaan mata mendapati berbagai tahap keterukkan 'vitreous veil' dan makulopati jejari roda (spoke-wheel maculopathy). Pengimbasan tomografi koheren optikal ke atas makula mengesahkan diagnosa ini. Ketiga adik beradik kemudiannya dirawat dengan ubat tittis mata; Brinzolamide untuk digunakan dua kali sehari. Pengimbasan tomografi koheren optikal diulangi enam and lapan belas bulan kemudian. Dari pemeriksaan klinikal didapati tiga mata dari ketiga-tiga beradik ini mempunyai ketajaman penglihatan yang stabil, manakala tiga mata lagi menunjukkan penambahbaikan dalam ketajaman penglihatan. Daripada tiga mata dengan ketajaman penglihatan yang stabil, satu darinya menunjukkan pengurangan retinoschisis dan dua mata yang lain menunjukkan retinoschisis yang semakin teruk. Sebaliknya, satu dari tiga mata dengan ketajaman penglihatan yang lebih baik telah mengalami pengurangan retinoschsis dan dua yang lain mengalami retinoschisis yang semakin teruk. Berdasarkan pemantauan klinikal, ketajaman penglihatan pesakit retinoschisis adalah tidak selaras dengan tahap kelekangan retina neurosensori. Rawatan retinoschisis adalah mencabar kerana tiada ubat atau kaedah terkini yang terbukti berkesan.


*Kata kekunci:* adik beradik, degeneratif makula, ketajaman penglihatan, retinoschisis juvana 'X-linked'

## Introduction

X-linked juvenile retinoschisis (XLRS) is a rare inherited bilateral vitreoretinal dystrophy which usually affects males early in life.[1] It is caused by a mutation of the *RS1* gene, which is responsible for encoding retinoschisin for intercellular adhesion. XLRS causes splitting of the retina. Splitting of the retinal nerve fiber layer and ganglion cell layers was reported in early histopathology studies.[2] However, with the development of spectral-domain optical coherence tomography (SD-OCT), the most common location of schisis cavities was reported to involve the inner nuclear layer, with occasional involvement of the outer plexiform and outer nuclear layers.[3] In this case series, we describe the clinical features as well as ophthalmoscopic and SD-OCT findings of three siblings with XLRS. Table 1 provides a summary of the cases.

*Table 1.* Summary of the clinical findings at first visit, 6 months, and 18 months

| | **Case 1** | | **Case 2** | | **Case 3** | |
|---|---|---|---|---|---|---|
| **Age (years)** | 5 | | 9 | | 7 | |
| **Laterality** | RE | LE | RE | LE | RE | LE |
| **Refraction** | +2.50 DS | +3.25 DS | +2.75 DS | +3.25 DS | +3.50 DS | +4.50 DS |
| **BCVA (First visit)** | 6/60 | 6/18 | 6/18 | 6/18 | 6/18 | 6/18 |
| **OCT (First visit)** | 362 µm | 363 µm | 535 µm | 510 µm | 501 µm | 404 µm |
| **BCVA (6 months)** | 6/120 | 6/18 | 6/18 | 6/18 | 6/24 | 6/36 |
| **OCT (6 months)** | 347 µm | 374 µm | 550 µm | 549 µm | 476 µm | 436 µm |
| **BCVA (18 months)** | 6/24 | 6/18 | 6/12 | 6/12 | 6/18 | 6/18 |
| **OCT (18 months)** | 347 µm | 379 µm | 566 µm | 577 µm | 475 µm | 439 µm |

BCVA: best-corrected visual acuity; RE: right eye; LE: left eye; DS: dioptres; OCT: optical coherence tomography

## Case presentation

**Case 1**

The first case concerns a 5-year-old full-term boy. The boy was initially referred for right eye strabismus at the age of 3 years. On examination, visual acuity (VA) in both eyes was 6/9.5 with Cardiff acuity test at 1 meter. Cycloplegic refraction showed hypermetropia of +2.75 diopters (DS) in both eyes. Cover test revealed alternating exotropia with left eye fixation, normal anterior segments, and no fundus abnormality. In view of good vision, no glasses were prescribed. The patient was given a 6-month appointment, but the boy defaulted to follow-up.

The boy was referred again by the Child Development Clinic 2 years after the first visit for poor vision in the right eye at 5 years of age. The mother denied worsening of the squint and she did not realize that her child was experiencing blurred vision. On examination, cycloplegic refraction revealed +2.50 DS in the right eye and +3.25 DS in the left eye. Best-corrected visual acuity (BCVA) was 6/60 in the right eye and 6/18 in the left eye. Cover test showed similar findings of alternating exotropia with left eye fixation. Bilateral anterior segment examinations were unremarkable. Bilateral fundus examination (Fig. 1a-b) revealed spoke-like striae radiating from the foveola

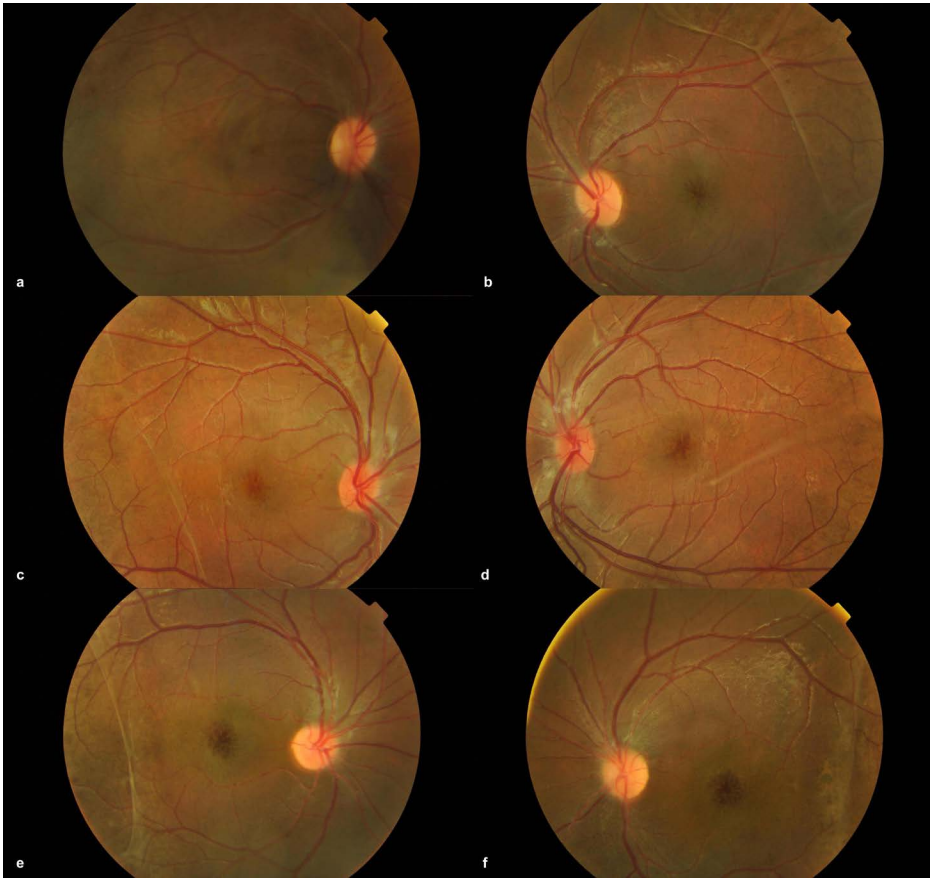


*Fig. 1.* Colour fundus photographs of the right and left eyes showing bilateral spoke-wheel appearance radiating from the foveola with blunted foveal reflex and vitreous veils. (*a*, *b*) Case 1; (*c*, *d*) Case 2; (*e*, *f*) Case 3.

with blunted foveal reflex, vitreous veils, and pigmentary changes of the retina. Bilateral macular SD-OCT (Fig. 2a-b) showed cystic spaces in the inner nuclear and outer nuclear layers, with loss of the foveal contour. Central subfield foveal thickness (CSFT) was 362 µm in the right eye and 363 µm in the left eye. He was diagnosed with alternating exotropia with left eye fixation, bilateral eye hypermetropia with right eye amblyopia, and bilateral eye XLRS. He was prescribed glasses and was started on left eye patching 2 hours per day as well as topical brinzolamide twice daily. In view of XLRS being an inherited disease, his two brothers (Case 2 and Case 3) and parents were asked to come for an eye screening. Both parents were screened with macular SD-OCT and their results showed normal retinal configuration with no signs suggestive of XLRS.

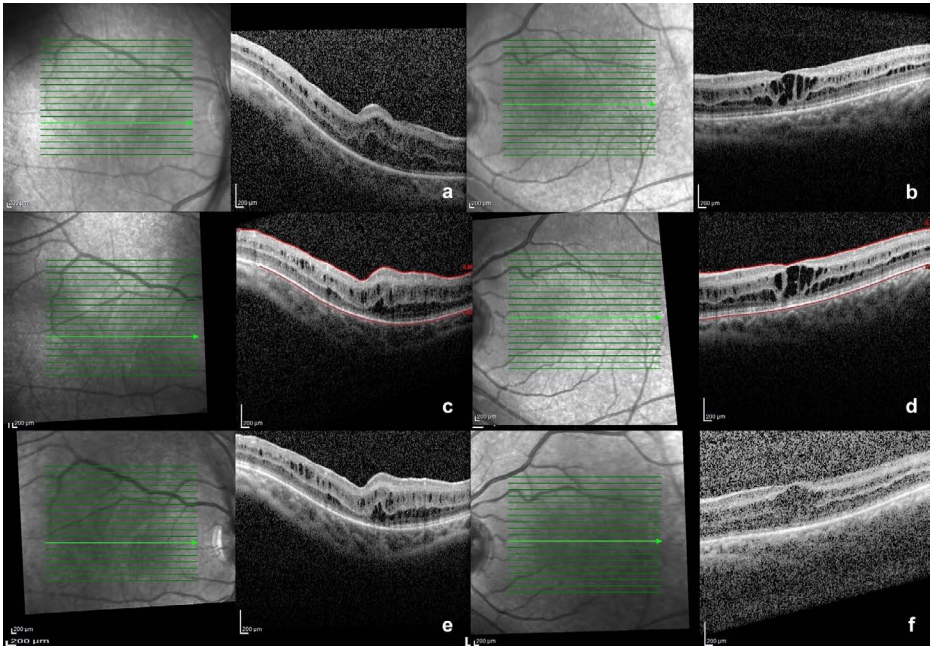


*Fig. 2.* Case 1: Optical coherence tomography images of the right and left eyes showing schisis cavities in the fovea of both eyes. (*a*, *b*) First visit; (*c*, *d*) at 6 months; (*e*, *f*) at 18 months.

Six months later, BCVA was 6/120 in the right eye and 6/18 in the left eye. Macular SD-OCT (Fig. 2c-d) showed CSFT in the right eye had improved from 362 µm to 347 µm, while the left eye had slightly worsened from 363 µm to 374 µm. Topical brinzolamide twice daily together with glasses and patching were continued. At 18 months, BCVA in the right eye improved to 6/24 while the left eye remained at 6/18. Macular SD-OCT (Fig. 2e-f) showed stable retinoschisis. CSFT was 347 µm in the right eye and 379 µm in the left eye. Hence, topical brinzolamide twice daily and patching were continued.

**Case 2**

A 9-year-old boy, the eldest of the three siblings, was brought for XLRS screening. He had been diagnosed with hyperopia by a private optometrist 2 years prior and had been prescribed spectacles. Further history revealed that he had complained of blurred vision for the past 2 years, even after refractive correction.

On examination, BCVA in both eyes was 6/18. Refraction showed +2.75 DS in the right eye and +3.25 DS in the left eye. Anterior segment examinations were unremarkable. Both fundi (Fig. 1c-d) showed spoke-wheel appearance of the macula with vitreous veils in the posterior pole. Bilateral macular SD-OCT (Fig. 3a-b) revealed cystoid spaces involving the inner nuclear and outer nuclear layers, with

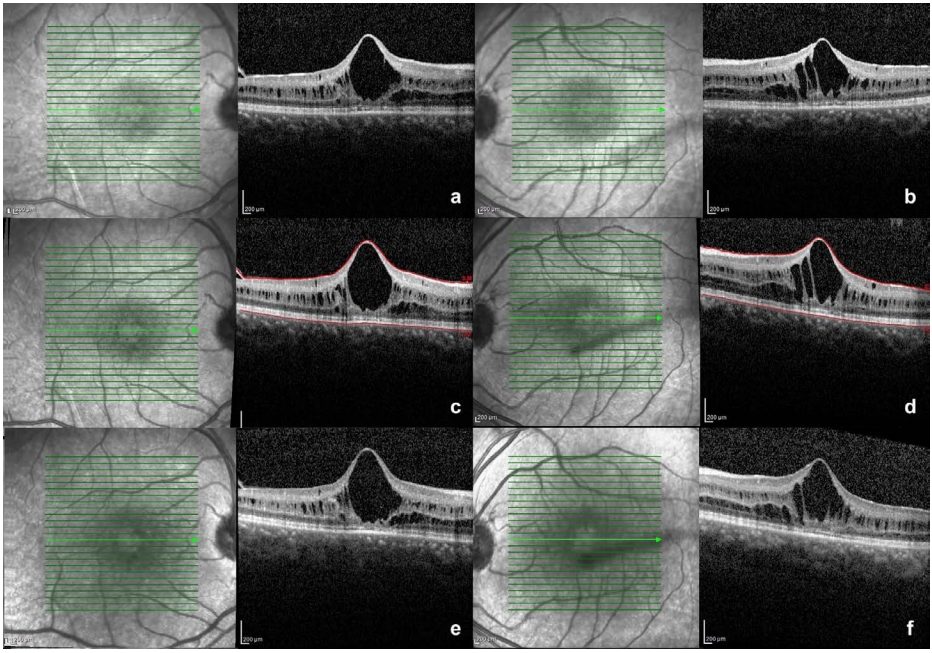


*Fig. 3.* Case 2: Optical coherence tomography images of the right and left eyes showing marked schisis cavities in the fovea of both eyes, with large bilateral foveal cysts. (*a, b*) First visit; (*c, d*) at 6 months; (*e, f*) at 18 months.

loss of foveal contour. CSFT was 535 µm in the right eye and 510 µm in the left eye. XLRS was diagnosed and he was started on topical brinzolamide twice daily.

Six months later, BCVA remained the same. Macular SD-OCT (Fig. 3c-d) showed worsening of bilateral eye retinoschisis with CSFT of 550 µm in the right eye and 549 µm in the left eye. At 18 months, bilateral BCVA improved to 6/12. Bilateral SD-OCT (Fig. 3-f) showed progression despite treatment. CSFT in the right eye increased to 566 µm and to 577 µm in the left eye. Topical brinzolamide was increased to three times daily.

**Case 3**

The third case was a 7-year-old boy, the sibling of the two boys mentioned above. He was also screened for XLRS. The child denied blurred vision or any other eye symptoms. On examination, cycloplegic refraction revealed +3.50 DS in the right eye and +4.50 DS in the left eye, with bilateral BCVA of 6/18. Ocular anterior segment examinations were normal. Similar to his brothers, his fundus examination (Fig. 1e-f) showed spoke-wheel appearance of the macula and vitreous veil involving the posterior pole in both eyes. There was also splitting of the retinal neurosensory layers by the cystoid spaces involving the fovea, as shown in the macular SD-OCT

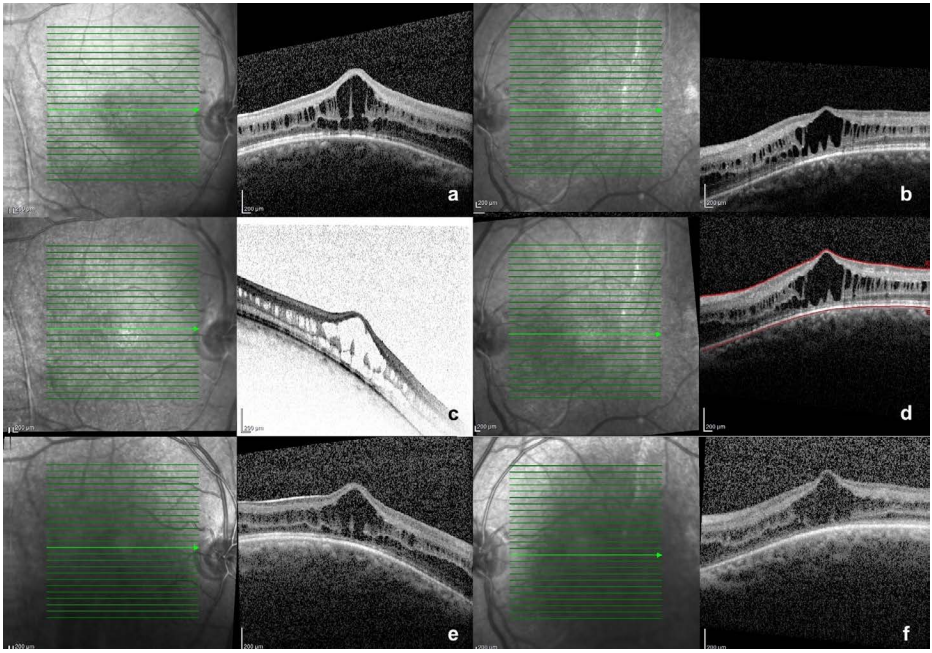


*Fig. 4.* Case 3: Optical coherence tomography images of the right and left eyes showing marked schisis cavities in the fovea of both eyes, with large bilateral foveal cysts. (*a, b*) First visit; (*c, d*) at 6 months; (*e, f*) at 18 months.

(Fig. 4a-b). CSFT was 501 µm in the right eye and 404 µm in the left eye. He was diagnosed with XLRS. Spectacle correction was prescribed and topical brinzolamide twice daily was started.

Six months later, the BCVA dropped to 6/24 in the right eye and 6/36 in the left eye. Macular SD-OCT (Fig. 4c-d) showed improvement of the retinoschisis in the right eye with CSFT reduced to 476 µm, but worsening of the retinoschisis in the left eye with CSFT of 436 µm. Topical brinzolamide was continued. At 18 months, bilateral BCVA was 6/18. No progression was seen on bilateral macular SD-OCT (Fig. 4e-f), with a CSFT of 475 µm in the right eye and 439 µm in the left eye. Topical brinzolamide twice daily was continued.

## Discussion

XLRS is the most common macular degenerative disease in boys and young men.[4] Females are usually asymptomatic carriers with incidental findings of minor retinal abnormalities during routine examination.[5] The pathogenesis of XLRS is due to a mutation of the *RS1* gene, which is responsible for encoding of retinoschisin.

Failure of retinoschisin formation will lead to failure of cell-cell adhesion, which can be seen clinically as splitting of the inner retinal layers.[6]

XLRS usually expresses symmetrically in both eyes; however, patients can present with a marked asymmetry of visual function.[7] Onset can be quite varied. It has been reported in infants as young as 3 months old. Patients may present with VA ranging from 6/6 to blindness. Several studies have shown that reduction of VA usually occurrs before puberty; subsequent VA may remain unchanged for many years in most cases.[1,8] In our first case, although both eyes expressed a similar degree of retinoschisis changes, VA in the right eye was far worse than the left eye. This could be due to the patient having right eye amblyopia secondary to alternating exotropia with left eye fixation. Thus, a trial of left eye patching 2 hours a day was started. After 18 months of patching, although there was no marked reduction of retinoschisis, BCVA in the right eye improved from 6/60 to 6/24. This explained the possibility of right eye amblyopia that improved with patching.

Hyperopia is commonly seen in patients with XLRS. Our patients had refractive errors ranging from +2.50 DS to +4.50 DS, which corresponds to a mean refractive error of approximately +2.5 DS found in most studies.[8]

XLRS is diagnosed with SD-OCT, which is fast, easy, and painless, and thus useful in children. Our youngest patient, who was only 5 years old, was cooperative enough for an SD-OCT examination, which can differentiate retinoschisis from retinal detachment. One study reported that foveal retinoschisis can be seen in 70% of XLRS patients, while peripheral retinoschisis is seen in 60% of XLRS patients.[9] Our three patients showed clinically characteristic foveal retinoschisis demonstrable on SD-OCT. Splitting of the retinal nerve fibre layer and ganglion cell layers was reported in early histopathology studies.[2] However, in recent studies, foveal schisis in the inner nuclear and outer plexiform layers are commonly present.[10,11] In our study, macular SD-OCT showed a similar pattern in all three cases, with the retinal split involving the inner and outer retina. Coalescing of these cystoid spaces in the fovea could cause further loss of VA in the future.

There is no definite treatment for XLRS currently. However, multiple studies have suggested that carbonic anhydrase inhibitors (CAIs) play an important role in reducing cystoid macular oedema in XLRS. CAIs increase fluid transport across the retinal pigment epithelium layer due to its inhibition of carbonic anhydrase present in the retinal pigment epithelium, thus reducing the cystoid spaces in the neurosensory retina and enhancing retinal adhesiveness.[12] Some studies have reported that 47% to 70% of XLRS patients showed reducted central retinal thickness after starting on CAIs.[13,14] A recent study by Verbakel *et. al* showed that response to CAIs (oral acetazolamide with or without topical CAIs) could be observed as early as 1 month after starting of treatment. Previous studies have also shown different responses to CAIs; improvement in BCVA was not always consistent with a reduction in the size of the macular cyst.[15] This might explain

why the changes in our patients' VA were not consistent with the improvement or worsening of the retinoschisis demonstrated on SD-OCT.

In this case series, three eyes showed stable VA and three eyes showed improved VA after starting topical brinzolamide twice daily. Out of the three eyes with stable VA, one eye showed improved retinoschisis while the other two eyes showed worsening retinoschisis. On the other hand, one out of the three eyes with improved VA had improved retinoschisis and the other two had worsening retinoschisis on SD-OCT. We could see that only two out of the six eyes had VA improvement and reduction in foveal thickness. Treatment with CAIs in our cases was not as promising as in other studies. We faced a few challenges in treating the three brothers, compliance being the main issue. The children were given topical brinzolamide twice daily initially because they needed to attend school. The mother admitted to forgetting to instil the topical brinzolamide occasionally. Furthermore, due to the COVID-19 pandemic, there were missed appointments and discontinuation of eye drops for a short period of time for all three brothers. Although the amount of eye drops instilled was the same for the three brothers, only Case 2 showed progression in CSFT at 18 months.

## Conclusion

XLRS is a rare inherited bilateral vitreoretinal dystrophy with no definite treatment currently. We found no direct correlation between macular thickness and BCVA in our case series. However, CAIs remain a treatment option, as some cases of XLRS may respond to CAI treatment.

## Declarations

**Ethics approval and consent to participate**
Not required.

**Consent for publication**

**Competing interests**
None to declare.

**Funding**
None to declare.

**Acknowledgements**
None to declare.

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*Case report*
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# Temporal macular thinning: a salient sign of Alport syndrome

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## Abstract

Alport syndrome is a hereditary, multisystemic disorder that causes abnormalities of the ear, kidney, and eye. A teenager who was suffering from end-stage renal failure and hearing problems was referred to us suspected of Alport syndrome. He did not have any ocular complaints and wore glasses for myopic astigmatism. His best-corrected visual acuity was 6/7.5 bilaterally. Anterior segment examination was unremarkable. Posterior segment examination showed perimacular dot-and-fleck retinopathy with bull's eye maculopathy. Optical coherence tomography revealed temporal macular thinning. The findings were in keeping with the diagnosis of X-linked Alport syndrome. Ocular findings can help diagnose Alport syndrome. Early detection and treatment can help delay the progression of kidney failure.

*Keywords:* Alport syndrome, dot-and-fleck perimacular retinopathy, temporal macular thinning

## Abstrak

Sindrom Alport adalah penyakit keturunan, melibatkan multisistem yang menyebabkan masalah pada telinga, ginjal, dan mata. Seorang remaja yang mengalami masalah ginjal di peringkat kritikal dan masalah pendengaran dirujuk kepada kami dan disyaki menghidap sindrom Alport. Dia tidak mempunyai keluhan okular dan memakai kacamata untuk astigmatisme rabun. Penglihatannya ialah 6 / 7.5 pada kedua-dua mata. Pemeriksaan segmen anterior tidak menpunyai

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sebarang masalah tetapi pemeriksaan segmen posterior menunjukkan retinopati titik-dan-flek perimakular dengan makulopati mata lembu. Tomografi koheren optik menunjukkan penipisan makula di bahagian temporal. Penemuan ini sesuai dengan diagnosis sindrom Alport yang berkaitan dengan pautan X. Penemuan okular dapat membantu mendiagnosis sindrom Alport. Pengesanan dan rawatan awal dapat membantu melambatkan kegagalan buah pinggang.

*Kata kunci:* penipisan makula temporal, retinopati titik-dan-flek perimakular, sindrom Alport

## Introduction

Alport syndrome (AS) is a rare genetic disorder caused by a mutation in collagen IV genes *COL4A3*, *COL4A4*, and *COL4A5,* which are primarily located in the basement membrane of the kidneys, eyes, and cochlea. AS can be transmitted as an X-linked, autosomal recessive, or autosomal dominant pattern. Among patients with AS, 85% are X-linked AS (XLAS) with a prevalence of 1 in 50,000 individuals and male preponderance.[1,2]

## Case presentation

A 14-year-old teenager suspected of AS was referred to us for ocular assessment by a nephrologist. The patient was under the specialist's follow-up for haematuria and had been diagnosed with end-stage renal failure. An otolaryngologist was also following the case for bilateral sensorineural hearing impairment since the age of 5; the patient was doing well with hearing aids. His paternal uncle had suffered kidney failure in his early 40s with an unknown cause. The patient had been offered genetic testing, but due to financial constraints, the option was not taken.

On ocular examination, best-corrected visual acuity was 6/7.5 (-5.50/-1.25 x 5) in the right eye and 6/7.5 (-5.25/-2.00 x 170) in the left eye. Anterior segment examination was unremarkable. There was perimacular dot-and-fleck retinopathy with bull's eye maculopathy on fundus examination of the right and left eye (Fig. 1A, B); Figure 1C shows a magnified view of the macula. Optical coherence tomography (OCT) showed temporal macular thinning of the right and left eye (Fig. 2). This supported the diagnosis of AS.

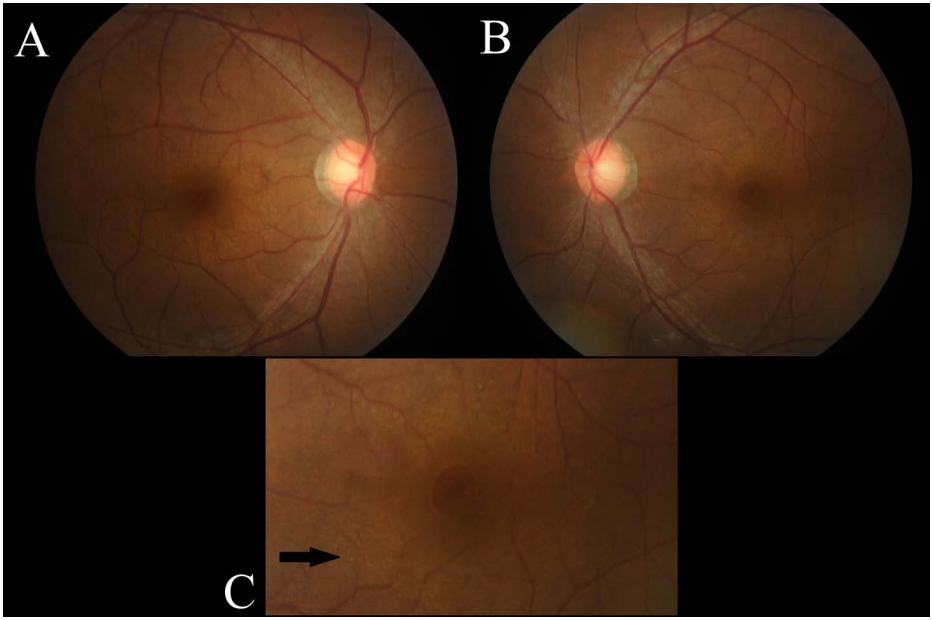


*Fig. 1.* Perimacular dot-and-fleck retinopathy in the right eye (*A*) and the left eye (*B*). (*C*) Magnified fundus photo shows perimacular yellowish dot-and-flecks retinopathy (arrow) with bull's eye maculopathy.

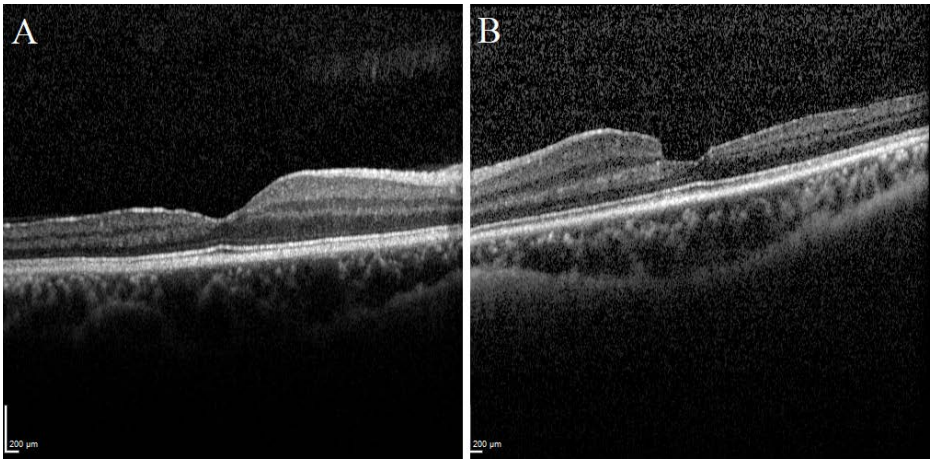


*Fig. 2.* Temporal macular thinning on optical coherence tomography in the right eye (*A*) and the left eye (*B*).

## Discussion

AS is a multisystemic, inherited disease characterized by hearing loss, haematuria, progressive renal failure, and ocular abnormalities. Ocular abnormalities result from mutation of collagen type IV, which is the most abundant protein found in the basement membranes of the cornea (Descemet's and Bowman's membranes), lens capsule, choroid (Bruch's membrane), and retina (inner limiting membrane).[1,3]

Ocular manifestations of AS include posterior polymorphous corneal dystrophy, recurrent corneal erosion, anterior and posterior lenticonus and cataracts, central and perimacular dot-and-fleck retinopathy, temporal macular thinning, dull foveal reflex (lozenge), bull's eye or vitelliform maculopathy, and lamellar or giant macular hole.[3,4]

Central or perimacular retinopathy is seen in 60% of men and 15% of women with XLAS.[5] The retinopathy manifests as scattered whitish-yellowish dots with variable density. These are amorphous deposits of acellular debris, lipids, and protein located between the pigment epithelium and Bruch's membrane. The retinopathies, like the other clinical features in AS, may depend on the direct effect of the underlying *COL4A5* mutations on the retinal basement membranes.[2,4] This finding becomes more prominent with time; however, visual acuity is substantially normal and no treatment is required.

Temporal macular thinning on OCT has been highlighted as the commonest ocular finding in X-linked and recessive AS, with an incidence ranging from 75–90% in males and 55–75% in females.[6] Kandon *et al.* reported a cohort of 32 patients with temporal macular thinning, which occurs frequently in male patients with XLAS; this specific sign helps not only for diagnosis but also for prognostication of XLAS.[5] Savige and colleagues had similar findings in their observation of 10 patients with Alport syndrome.[1]

Ocular manifestation is exceptionally helpful in predicting the inheritance pattern of AS in a diagnostic dilemma when genetic testing is not readily available. As in our case, confirmatory genetic testing was turned down due to unaffordable cost. With the availability of noninvasive OCT, temporal macular thinning can be easily detected, contributing to the diagnosis of AS and its inheritance. In a condition where genetic testing and renal biopsy are not feasible, macular OCT is the cheapest, painless, and most readily available investigation that can aid of diagnosis of AS. Macular OCT showing temporal thinning can provide a hint to clinicians to investigate further for XLAS, as other ocular signs can be subtle, and clinicians might miss the diagnosis.

Chen *et al.* reported that temporal macular thinning is associated with younger age of onset of renal failure.[7] Early onset of renal failure is usually progressive, leading to end-stage renal failure requiring a renal transplant. Ophthalmological findings are thus crucial in the early diagnosis of XLAS. Although it has no implication on vision, early detection improves prognosis. Timely treatment with

angiotensin-converting enzyme inhibitor helps in slowing the deterioration and inevitable progression to end-stage renal failure, which could relatively improve life expectancy.

## Conclusion

Temporal macular thinning together with dot-and fleck-retinopathy are salient signs that can help in the diagnosis of XLAS. These signs can also predict the prognostic value in determining the nature of renal failure which commonly progressive and if treated early can delay the onset of end-stage renal failure.

## Declarations

### Consent for publication

Informed consent for the publication of the patient's images and clinical data was obtained from the patient's parents.

### Funding

None to declare.

### Competing interests

None to declare. Conflict of interest statements were attached with the manuscript submission.

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# Occlusive retinal vasculitis in an immunocompetent woman: rare presentation of ocular melioidosis

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## Abstract

*Burkholderia pseudomallei* is a known great mimicker responsible for melioidosis. Melioidosis presents with a wide spectrum of clinical presentations in various organs including the eye. Ocular involvement in melioidosis is unusual, with eyelid and orbital infection as the commonest presentation. We describe a 41-year-old, healthy woman who complained of reduced vision in her left eye. On examination, vision in the left eye was 6/9. There was evidence of occlusive retinal vasculitis on fundoscopy examination. Fundus fluorescein angiogram showed extensive capillary fallout. Diagnosis was established by a rise in the serum antibody titre for the bacterium and further supported by clinical improvement of vision after completion of treatment antibiotics: third-generation cephalosporin and combination of amoxicillin and clavulanic acid. Sectoral panretinal photocoagulation at the capillary fallout area successfully arrested the sequelae of retinal ischaemia. Occlusive retinal vasculitis is a rare presentation of melioidosis. Early prompt diagnosis of ocular melioidosis in an immunocompetent individual helps prevent visual-related morbidity. The ability of this bacteria to cause recurrent infection in an endemic area should not be underestimated.

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*Keywords:* Burkholderia pseudomallei, immunocompetence, melioidosis, occlusive retinal vasculitis


# Abstrak

Burkholderia pseudomallei adalah organisma yang dikenali sebagai peniru yang agung adalah penyebab penyakit meliodosis. Meliodosis mempunyai spektrum klinikal yang meluas melibatkan pelbagai organ termasuk mata. Walaubagaimanapun penglibatan mata dalam penyakit ini adalah agak jarang berlaku. Sekiranya berlaku, jangkitan sering terjadi pada kelopak mata dan orbit. Di sini, kami memerihalkan seorang wanita yang sihat berumur 41 tahun yang menghadapi masalah kurang penglihatan pada mata kirinya. Pemeriksaan mata mendapati penglihatan pada mata kirinya adalah 6/9. Funduskopi mendapati terdapat bukti radang dan penyumbatan pada salurdarah retina. Ujian angiogram floresein fundus (fundus fluorescein angiogram [FFA]) menunjukkan keguguran atau penyumbatan kapilari secara meluas. Diagnosa dibuat berdasarkan kenaikkan titer antibodi dalam serum dan juga keberkesanan ke atas penglihatan mata setelah rawatan antibiotic diberikan iaitu generasi ketiga cefalosporin dan gabungan amoxicillin dan asid klavulanik. Kesan iskemia retinal dapat di hentikan dengan rawatan fotokoagulasi secara sektoral pada kawasan kapilari yang tersumbat. Radang dan penyumbatan salur darah retina adalah manifestasi klinikal yang amat jarang berlaku bagi meliodosis.


*Kata kekunci:* Burkholderia pseudomallei, kompeten imuniti, meliodosis, radang dan penyumbatan salurdarah

## Introduction

Melioidosis is an infectious disease caused by a gram-negative, motile, non-spore forming facultative anaerobic bacillus known as *Burkholderia pseudomallei*.[1] Melioidosis presents with a broad spectrum of clinical presentations and organ involvement.[2] It can vary from a latent infection with an incubation period of up to 29 years to fulminant sepsis with a high mortality rate.[3] Ocular involvement in melioidosis is rare and has devastating outcomes.[2]

Here we report a case presenting with occlusive retinal vasculitis secondary to melioidosis. We discuss possible appropriate early treatment and visual outcome in this rare ocular disease in an immunocompetent adult.

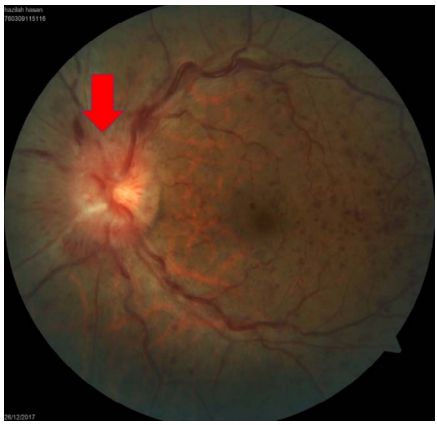

*Fig. 1.* Fundus photograph showing swollen (irregular margin) and hyperemic optic disc of the left eye.

## Case presentation

A 41-year-old, healthy woman presented with reduced vision in the left eye for 2 weeks. There was no ocular pain, redness, or discharge. She provided a history of contact with a pulmonary tuberculosis patient several years prior. There was no history of recent travel abroad, swimming in waterways, or any significant skin abrasion wound. She denied any productive cough, tachypnoea, or haemoptysis. She was afebrile and systemic review was unremarkable. She stated she enjoyed gardening in her free time.

On examination, vision in the left eye was 6/9 and 6/6 in the right eye. There was no relative afferent pupillary defect. Anterior segments of both eyes were unremarkable. Her left fundus showed a swollen, hyperaemic optic disc as well as multiple splinter haemorrhages with tortuous and dilated vessels (Fig. 1). There was also a vasculitic lesion seen on the optic disc. Multiple dot blot haemorrhages were seen in all four quadrants of the fundus. The macula appeared normal, without evidence of macula oedema. The vitreous was clear.

Thorough investigations were conducted, including connective tissue disease screening and computed tomography scan of the orbit, which were all negative. Mantoux test was negative and erythrocyte sedimentation rate was not elevated. Her chest X-ray and electrocardiography (ECG) appeared normal. There was positive IgM titre for *B. pseudomallei* (1:320). However, there was no clinical sign to suggest systemic melioidosis infection. Fundus fluorescein angiography (FFA) showed leakage from the disc vessels and small vessel vasculitis with extensive areas of capillary fallout (CFO), suggestive of occlusive vasculitis (Fig. 2). Sectoral pan retinal photocoagulation was done at the area of capillary nonperfusion (Fig. 3).

She was initially treated empirically as presumed ocular tuberculosis based on clinical presentation, but treatment was stopped due to deranged liver enzymes.

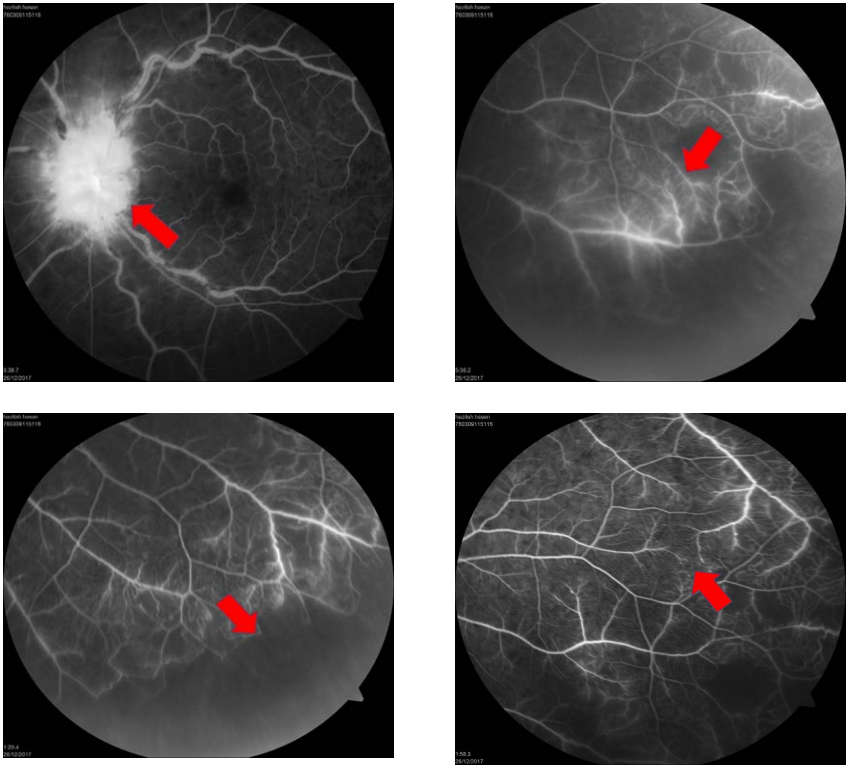

*Fig. 2.* FFA showing presence of leakage from the optic disc, extensive area of capillary fallout and small vessels vasculitis.

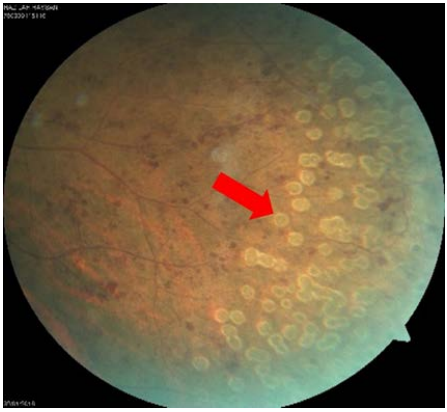

*Fig. 3.* Fundus photograph showing area of sectoral panretinal photocoagulation of the left eye.

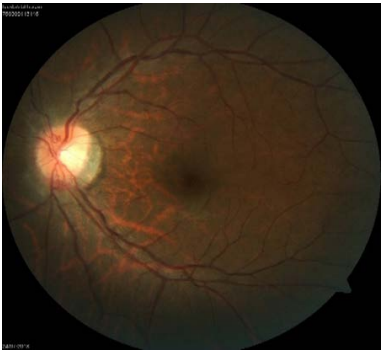

*Fig. 4.* Fundus photograph showing regular margin of disc (swelling resolved) and pink colored disc. There was no more haemorrhages seen and normal looking retinal vessels.

Following the raised IgM titre for *B. pseudomallei*, she was then treated with intravenous ceftazidime for 2 weeks followed by oral amoxicillin-clavulanic acid. Her vision improved to 6/6 and the optic disc swelling improved markedly (Fig. 4).

## Discussion

Melioidosis is a multisystemic infectious disease caused by the gram-negative soil saprophyte *B. pseudomallei*, which is commonly found in contaminated water and soil. Melioidosis is endemic in Malaysia and other Southeast Asian countries and is responsible for high case-fatality rates.[4] Infection is acquired by inhalation of dust, ingestion of contaminated water, and contact with contaminated soil, especially through skin abrasions.[5,6] However, in endemic areas such as Malaysia, transmission can have several modes of entry. Thus, absence of skin abrasions may not exclude the possibility of melioidosis, as in this case. In fact, there was reported case of transmission through inhalation during the flight training in Singapore and monsoon season in Philippines.[7,8] There were also reported cases of endophthalmitis following history of swimming in waterfalls in Malaysia.[9]

In the present case, there was no specific risk factor of exposure except for working with soil while gardening. The risk of melioidosis is reportedly higher in those with systemic diseases such as diabetes mellitus.[7,10] Although immunocompromised status increases the risk, there have been reported cases among healthy individuals as in this case.[11] In Malaysia, 15–42% of melioidosis cases reported had no significant risk factors.[10]

In general, the clinical spectrum of melioidosis is wide, ranging from mild symptoms of flu-like illness to fatal septicaemia.[8] Ocular manifestation is rare. The most common reported presentation is lid abscess and its sequelae: preseptal and orbital cellulitis.[2,12,13] There was also a reported case of endophthalmitis in children with history of swimming in a waterfall.[9] However, there have been no reported cases with direct retinal involvement.

Here, we reported a case of occlusive retinal vasculitis with positive serological detection of *B. pseudomallei*. We postulated that the septic bolus or embolus formed by this 'great mimicker' occluded the retinal vein and impeded blood flow. Symptoms were lacking to suggest recent infection and potential sites of entry were absent, pointing towards recurrence or relapse. The ability of *B. pseudomallei* to evade the immunological radar of human protective mechanisms and reach a dormant stage may explain the lack of symptoms. The question remains as to when the patient was initially infected. There are many suggested classifications or categories due to the nonspecific clinical presentation of melioidosis.[8,10] Based on the review on melioidosis in Malaysia,[10] her presentation was similar to the category of acute localized infection and remained localized without bacteraemic stage. She was perhaps partially treated with amoxicillin-clavulanate during the initial stage of

localized infection, which may have presented as severe flu-like illness, long before this current infection. Perhaps, due to the unspecific presentation of melioidosis, this condition went unnoticed by this patient.

The next question is where these septic embolus and bolus originated. Septic emboli may originate from other parts of the body or direct formation in the retinal vein. There have been reported cases of mycotic abdominal pseudoaneurysm, pericardial effusion, and heart valve vegetation in Malaysia.[11,14] Clinically, there was no sign to suggest heart abnormalities based on the patient's ECG. ECG and Doppler sonography of the carotid artery was not conducted due to lack of indication in her case. Since the retinal vasculature is an end artery, a small primary or secondary embolus may impede the blood supply, causing occlusive retinitis. The presence of CFO on FFA indicated retinal vein obstruction and ischaemia. In the presence of retinal ischaemia, regardless of the cause, sectoral panretinal photocoagulation is indicated.[15]

The patient's history of contact with tuberculosis may have been a red herring and delayed the appropriate treatment. There have been reported cases of melioidosis mimicking tuberculosis.[16] In addition, confirmation of *B. pseudomallei* is also challenging. The definitive diagnosis is based on culture of the organism from blood, sputum, urine, or pus. However, where the foci of infection are unknown or inaccessible to standard specimen collection techniques, (which occurs most commonly in subacute or chronic cases), nonbacteraemic melioidosis, diagnosis is made by serology.[1] In Malaysia, current practice is using serological diagnosis with the optimized in-house ELISA as the method of choice for recent exposure to *B. pseudomallei*. Although the accuracy of this method remains to be proven, it is widely acceptable in Malaysia.[17] Other modes of detection include indirect haemaglutination or complementary test, and recently, molecular diagnostic testing.

In this case, the IgM ELISA was elevated (1:320), which was considered as positive. No samples were taken from ocular fluids, including the vitreous. However, the elevated serum titre was considered adequate for initiation of treatment. In addition, the treatment showed clinical improvement in visual acuity and retinal findings. The patient's vision remained good until the time of writing.

## Conclusion

Although not common, ocular melioidosis may be associated with devastating morbidity without proper management. Occlusive retinal vasculitis due to *B. pseudomallei* is rare. High index of suspicion in endemic areas, even in immunocompetent individuals, is important for initiation of early treatment and preservation of vision.

## Declarations

### Ethics approval and consent to participate
Not required.

### Consent for publication
The patient provided informed consent for the use of the clinical images and information contained in this case report.

### Competing interests
None to declare.

### Acknowledgements
None to declare.

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*Case report*
*https://doi.org/10.35119/myjo.v3i3.133*

# Orbital apex syndrome secondary to sinonasal diffuse large B cell lymphoma: how rare is it?

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## Abstract

A sinonasal lymphoma is an uncommon form of non-Hodgkin lymphoma (NHL), comprising only 1.5% of all lymphomas. Here, we report a rare case of primary sinonasal diffuse large B cell lymphoma (DLBCL) found accompanying orbital apex syndrome. A 75-year-old Chinese man presented with progressively reduced visual acuity in the left eye for over 2 months. He also complained of frequent rhinorrhoea for the previous 4 months. Upon examination, his left eye was noted with poor vision with incomplete ptosis, periorbital fullness, and ophthalmoplegia. Laboratory findings were within normal limits. Computed tomography scan of the brain and orbit showed nasal soft tissue mass with local extension to the left extraconal space. Histopathological examination of the nasal biopsy tissue showed high-grade DLBCL. The distal cranial neuropathy caused by the lymphomatous infiltration of the left paranasal sinuses had preceded the systemic manifestation. The patient was initiated on chemotherapy and has been, at the time of writing, in remission for 8 months after presentation.

*Keywords:* diffuse large B cell lymphoma, orbital apex syndrome, sinonasal lymphoma

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# Abstrak

Limfoma sinonasal adalah bentuk limfoma bukan Hodgkin (NHL) yang jarang dijumpai, melibatkan hanya 1.5% daripada semua jenis limfoma. Kami melaporkan satu kes sinonasal primer limfoma sel B besar (DLBCL) yang menyebar yang jarang ditemui yang mengiringi sindrom apeks orbital. Seorang lelaki Cina berusia 75 tahun mengalami tahap penglihatan kiri yang semakin menurun selama lebih dari 2 bulan. Dia juga mengadu kerap mengalami rhinorrhea sejak 4 bulan yang lalu. Setelah diperiksa, tahap penglihatan mata kirinya adalah lemah beserta ptosis separa, bengkak kawasan periorbital dan oftalmoplegia. Semua keputusan makmal adalah normal. Imbasan tomografi (CT) otak dan orbit menunjukkan ketumbuhan tisu lembut hidung dengan perebakan setempat ke ruang ekstrakonal kiri. HPE tisu biopsi hidung menunjukkan DLBCL gred tinggi. Neuropati kranial distal yang disebabkan oleh penyusupan limfomatosa sinus paranasal kiri telah mendahului manifestasi sistemik. Pesakit telah dirawat dengan kemoterapi dan kini telah 8 bulan dalam fasa pemulihan.


*Kata kekunci:* limfoma sel B besar yang tersebar, limfoma sinonasal, sindrom puncak orbital

## Introduction

Approximately 70–80% of non-Hodgkin lymphomas (NHLs) are nodal lymphomas; the most common extranodal sites involved are the gastrointestinal tract (34%), followed by head/neck (14%) and skin (11%).[1] One of the rarest extranodal sites (0.44%) is the sinonasal tract.[2] The prevalence of sinonasal lymphoma is 0.37% of all extranodal NHL sites.[3] These tumours are rare in Asia; this is reflected in the scarcity of literature that reviewed outcomes for the Asian cohorts with sinonasal lymphoma.

## Case presentation

In June 2019, we evaluated a 75-year-old Chinese male with a history of hypertension. He experienced progressive visual loss in the left eye and retro-orbital pain for 2 months, accompanied by frequent rhinorrhoea for the past 4 months.

Compared with his right eye, visual acuity in the left eye was markedly reduced (OD 6/12, OS counting fingers). The left pupil showed 4+ relative afferent pupillary defect. The patient also exhibited periorbital fullness, mild proptosis, and incomplete ptosis of the left upper eyelid (Figs. 1 and 2). Left eye motility was limited in upgaze, downgaze, and adduction (Fig. 3). General physical examination was unremarkable.

A computerized tomography (CT) scan revealed a soft tissue lesion in the bilateral

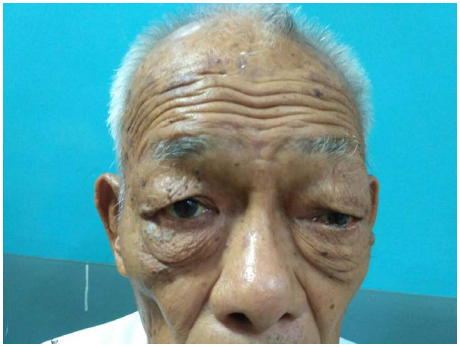

*Fig. 1.* Left eye fullness and proptosis

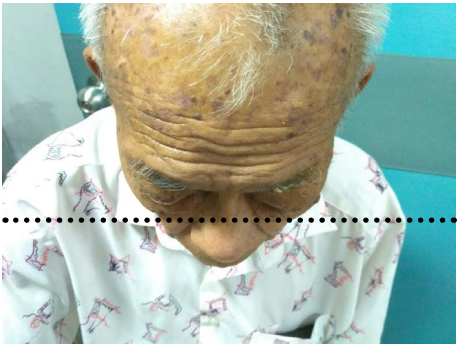

*Fig. 2.* Clinical Photography in primary position showing ptosis in the patient's left eye.

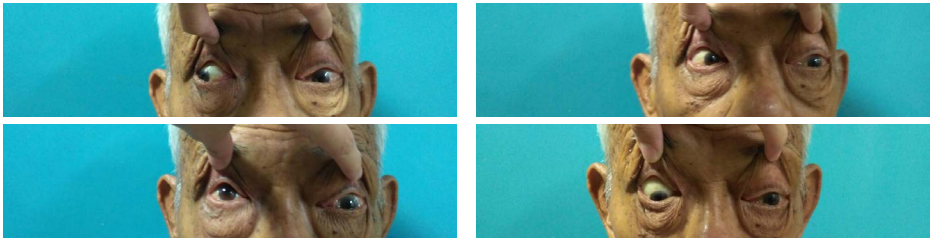

*Fig. 3.* Four gaze photo of a patient with orbital apex syndrome showing limitation of motility in left eye elevation, depression, abduction and adduction.

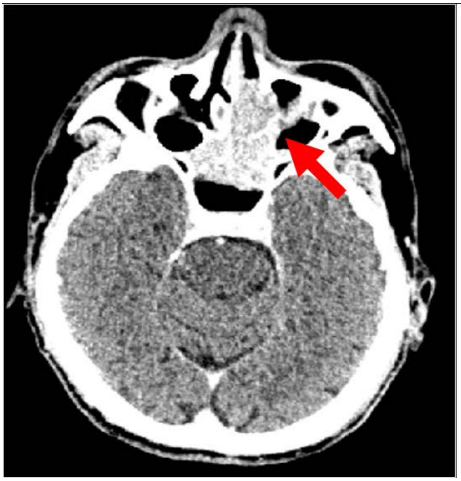

*Fig. 4.* CT scan showing a soft tissue lesion in the bilateral posterior nasal cavity, ethmoidal, sphenoid and left frontal sinuses extends into left extra-conal space.

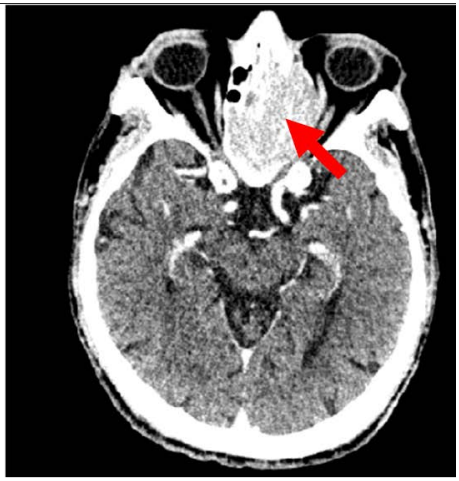

*Fig. 5.* This mass partially obliterating the left optic canal, displacing left medial rectus muscle.

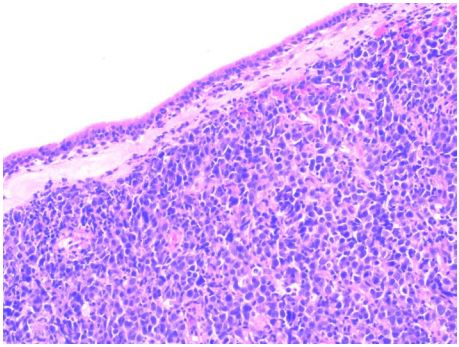

*Fig. 6.* The hematoxylin and eosin (H&E x100) stained slides of section from nasal tissue mass showing malignant lymphoid cells exhibiting severe nuclear pleomorphism diffusely infiltrating the tissue.

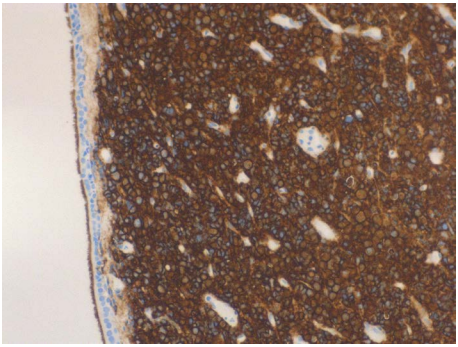

*Fig. 7.* On immunohistochemistry (IHC) stain showing the lymphoma cells are positive for CD20.

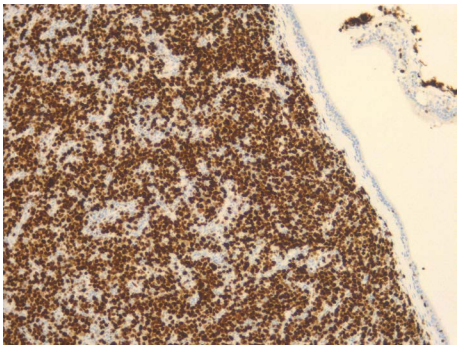

*Fig. 8.* On immunohistochemistry (IHC) stain showing the lymphoma cells are positive for Ki67; Proliferative index 90%.

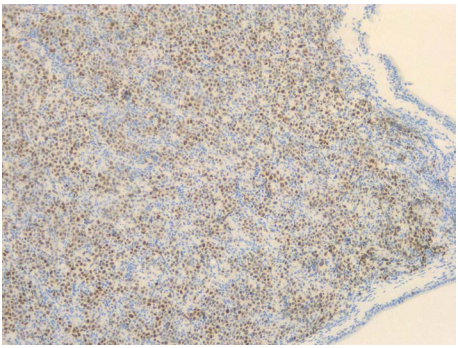

*Fig. 9.* On immunohistochemistry (IHC) stain showing the lymphoma cells are positive for c-Myc (50%).

posterior nasal cavity, ethmoidal, sphenoid, and left frontal sinuses extending into the left extraconal space. This mass partially obliterated the left optic canal, displacing the left medial rectus muscle; associated with bony erosion and local extension (Figs. 4 and 5).

The patient was referred to an ENT specialist; diagnostic nasal endoscopic examination and a biopsy were performed. Histopathological findings confirmed the diagnosis of high-grade diffuse large B cell lymphoma (DLBCL). Tumour cells were immunepositive for C-myc, BCL-2, and BCL-6 (Figs 6–9). Staging workup showed no metastases.

The patient received 12 cycles of chemotherapy consisting of R-CHOP regimen

over 6 months. Visual acuity, ptosis, and ocular motility improved after 6 months, and CT showed a marked reduction of the primary sinonasal tumour with minimal residual lesion within the left nasal cavity and left ethmoid sinus; the rest of the sinuses were clear with unremarkable orbits, optic nerve, and optic canal.

## Discussion

This case report highlights the challenges associated with the diagnosis and treatment of patients with sinonasal DLBCL. Sinonasal DLBCL develops gradually within a confined anatomic space; the initial signs and symptoms are known to be subtle and often mimic those of benign inflammatory diseases. According to Yen *et al.*, the average duration between a patient's awareness of symptoms and their decision to seek medical help was 8.9 months.[4] Patients tend to ignore their symptoms until alerting symptoms continue to develop, whereby the neoplasm reaches a considerable size or involves the adjacent anatomical structures.

In comparison to T-cell lymphoma, which is mostly diagnosed at an early stage, B-cell lymphoma is usually diagnosed at a late stage. T-cell lymphoma is commonly located in the nasal cavity and results in nasal symptoms earlier, whereas B-cell lymphoma found in sinuses very often induces symptoms only after extension to surrounding structures.[4] Besides, B-cell lymphoma is usually associated with bone destruction, particularly in the orbital region, frequently causing proptosis and cranial neuropathy.

The bony orbital apex is formed by the optic canal, which comprises the oculomotor nerve (III), trochlear nerve (IV), abducens nerve (VI), and the ophthalmic branch of the trigeminal nerve (V1) in association with optic nerve dysfunction. The damage to these structures results in orbital apex syndrome, as demonstrated in our case.

The primary treatment for nasal DLBCL is chemotherapy; R-CHOP is the standard treatment regimen. Rituximab, a monoclonal anti-CD20 antibody, is known to improve remission rates and overall survival of patients with DLBCL, especially in patients with tumours overexpressing the BCL-2 protein. Our patient was given 12 cycles of R-CHOP and a good outcome was observed.

## Conclusion

Heightened clinical suspicion in any patient with a history of chronic rhinorrhoea in combination with cranial neuropathy or orbital symptoms is vital for early detection and timely management. Chemotherapy with R-CHOP is highly effective, but longer follow-ups are needed.

## Declarations

Any opinions, findings, conclusions, or recommendations expressed in this material are those of the authors and do not reflect the views of the Ministry of Health Malaysia.

**Consent for publication**
The patient provided informed consent for use of his images and clinical data in this case report.

**Competing interests**
The authors declare no competing interests regarding the publication of this case report.

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**Acknowledgements**
None to declare.

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*Eye-Quiz*

# Blood-stained cornea

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## Clinical context

A 42-year-old man who had suffered from a corneal laceration with grade 3 traumatic hyphaema underwent corneal suturing and anterior chamber washout. However, after the procedure he developed recurrent grade 2 hyphaema. Eventually, the hyphaema resolved completely after 9 days of medical management.

**Question 1**
What is the pathophysiology of condition seen in Figure 1a and Figure 1b?

**Question 2**
What is the indication for surgical intervention in traumatic hyphaema?

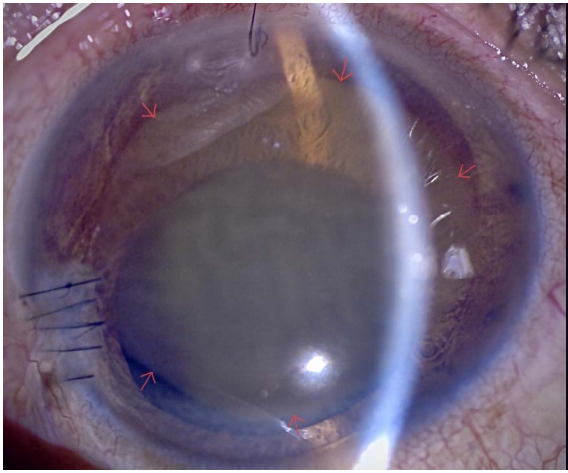

*Fig. 1a.*

*Fig. 1b.*

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**Answer 1**

Prolonged hyphaema with high intraocular pressure (IOP) can lead to corneal blood staining. The erythrocytic breakdown products penetrated the discontinuous endothelium and intact Descemet's membrane embedded in the posterior stroma, whereas hemosiderin deposited in the anterior stroma. It is a reversible process whereby the clearing started from the periphery followed by the centre.[1]

**Answer 2**

Timing and indications for surgical intervention:

1. To prevent corneal blood staining:
   - IOP ≥ 25 mmHg for 5 days with total hyphaema or hyphaema that does not resolve below 50% at 6 days.[2,3]
   - Evidence of early corneal blood staining.
2. To prevent optic atrophy:
   - IOP averages > 60 mmHg for more than 2 days.[2]
   - IOP averages > 35 mmHg for 7 days.[3]
   - IOP averages ≥ 25 mmHg for more than 24 hours or repeated transient spiking of IOP > 30 mmHg for 2 to 4 days despite maximum medical therapy in sickle cell disease.[2]
3. To prevent peripheral anterior synechiae formation
   - Total hyphaema that persists for 5 days.
   - Hyphaema failing to resolve to less than 50% of the anterior chamber volume by 8 days.[2]

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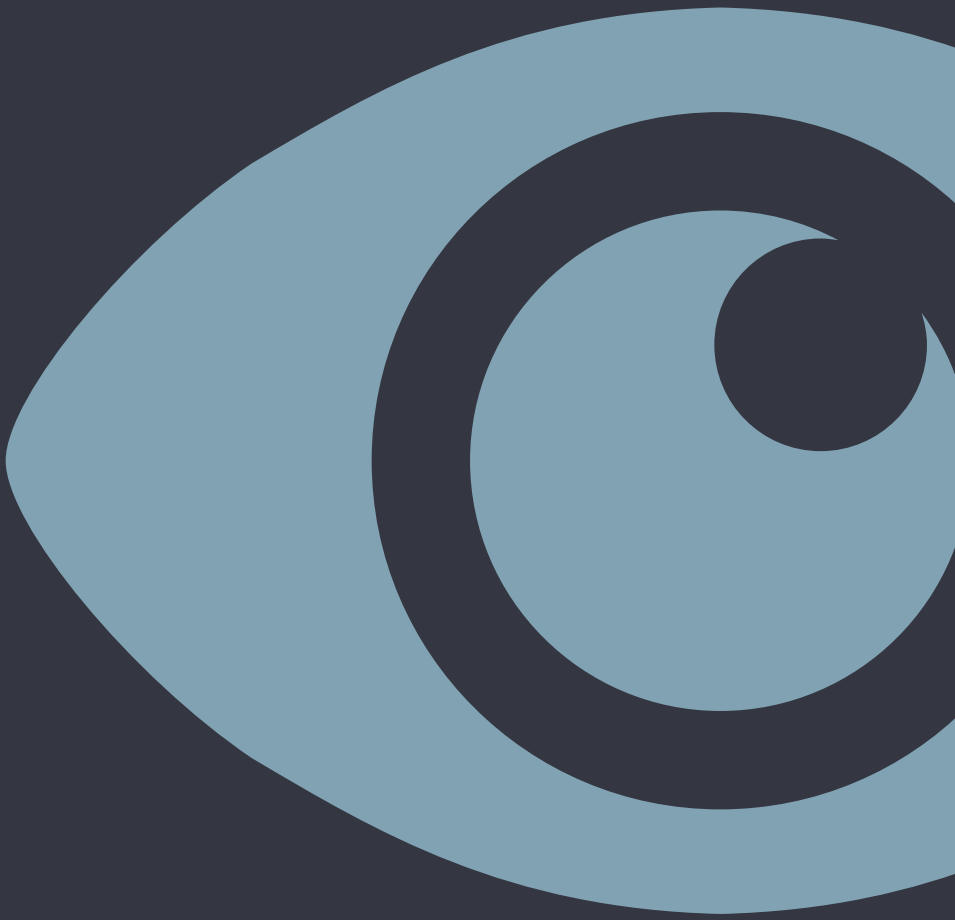

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